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Epidemiological insights in management of aneurysmal subarachnoid hemorrhage

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Karlijn van Donkelaar

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Chapter 1.

General introduction

Epidemiology and etiology

Non-traumatic subarachnoid hemorrhage (SAH) is a devastating type of stroke, accounting for 5% of all strokes.¹ It is characterized by the extravasation of blood into the subarachnoid space, the area between the arachnoid and the pia mater, which is filled with cerebrospinal fluid and covers the central nervous system. The average incidence of SAH is 9.1 per 100.000 people annually and the highest incidence rates are reported in Japan and Finland, with respectively 22.7 and 19.7 cases per 100.000 people annually.² Mortality rates after SAH are significant (35%), while one-third of the survivors remain functionally dependent, also in the long-term.³ Due to the relatively young age at which SAH usually occurs (mean 55 years), the loss of productive life years from SAH is comparable with that of ischemic stroke even though the latter has a much higher incidence.³

An intracranial aneurysm, mostly located in the circle of Willis (figure 1), is the most frequent cause of spontaneous subarachnoid hemorrhage, accounting for 85% of all cases.⁴ In the remaining 15% of patients, no symptomatic aneurysm can be detected. Two-third of these cases is considered to be a so-called non-aneurysmal perimesencephalic hemorrhage, with the presence of blood typically limited to the subarachnoid spaces around the midbrain (i.e. mesencephalon).⁴ This is a relatively benign type of SAH.⁵ In the other one-third of the cases, either no cause (non-aneurysmal SAH) or a relatively rare cause can be detected, such as an intracranial artery dissection, arteriovenous malformation, (inflammatory) disorder of the cerebral blood vessels, a bleeding disorder or a bleeding caused by an intracranial tumor.⁶

Figure 1 | The circle of Willis and its branches (adopted from "Atlas of Human Anatomy", Netter F.H., 2014, p. 143-144, Elsevier Health Sciences)

Intracranial aneurysms develop during the course of life and are not present at birth, as once was believed. The incidence of intracranial aneurysms among average adults is around 3% and increases with age.⁷ Due to improving imaging techniques and the increasing use of cranial imaging, they are more frequently detected, but most of these aneurysms will never rupture. The risk of rupture increases with the size of the aneurysm, as well as with the presence of risk factors such as hypertension, smoking, the use of sympathomimetic drugs and excessive alcohol intake.⁸ Also women are more likely to have a SAH, as well as people with a (family) history of SAH and certain genetic syndromes such as polycystic kidney disease.⁸ Despite the extensive knowledge about risk factors for SAH, the underlying mechanism of aneurysm formation and rupture is not completely understood.

Symptoms and diagnosis

The classic symptom of SAH is a thunderclap headache; a headache developing over a few seconds.⁹ Neck stiffness, vomiting, confusion, lowered level of consciousness and seizures are other well-known symptoms. In case of compression of a cranial nerve by an aneurysm or an associated hematoma in the brain parenchyma, focal neurological deficits can occur.⁶ The presentation of a patient with SAH varies considerably, some patients present complaining of a severe headache, other enter in a comatose condition. In approximately 10% of the cases, the patient dies before reaching the hospital.³

If a SAH is suspected, imaging with cranial computerized tomography (CT) scan without contrast is examination of first choice, as blood can be easily detected. In a minority of cases (3%), the initial CT scan is false negative for subarachnoid blood.⁴ Consequently, it is common practice to perform a diagnostic lumbar puncture (LP) after a negative scan, at least 12h after the occurrence of symptoms. In case of presence of subarachnoid blood, spectrophotometry can then confirm the presence of bilirubin in the cerebrospinal fluid (CSF).⁴ Nowadays, advances in magnetic resonance imaging (MRI), can often allow the diagnosis of SAH to be made in case of a negative cranial CT scan, avoiding the need for an invasive LP.⁷ After the diagnosis of subarachnoid blood, angiography is required to detect the underlying cause, notably the presence of a symptomatic aneurysm. Digital subtraction angiography (DSA) is still regarded the golden standard, however, it is an invasive and time-consuming procedure and associated with risks for complications such as ischemia and rebleeding of the aneurysm. Nowadays, CT-angiography (CTA) and MR-angiography (MRA) are more convenient. CTA can easily be performed immediately after the initial CT-scan.

Treatment

In patients with an aneurysmal SAH (aSAH), aneurysm repair is required to prevent recurrent bleeding of the aneurysm (a so-called rebleeding). Aneurysm repair is instigated soon after aSAH, but exact timing is depending on several factors, not only logistical factors such as referral time to a neurovascular center and availability of treatment modalities, but also the clinical condition of the patient. The clinical condition is most frequently indicated by the World Federation of Neurosurgical Societies (WFNS) SAH grading scale (table 1).¹⁰ This scale is based on the Glasgow Coma Scale (GCS), which measures the level of consciousness, in addition to the presence or absence of neurological deficits such as aphasia or (hemi)paresis.

Patients with grade IV and V are regarded to be in a poor clinical condition, which is associated with a poor prognosis.¹¹ As a decreased level of consciousness can be caused by several early aSAH complications such as acute hydrocephalus, neurological resuscitation is required to properly assess the patient's clinical condition. In case of acute hydrocephalus, immediate cerebrospinal fluid (CSF) drainage with an external ventricular of lumbar drain is necessary.⁸ A space-occupying intracerebral hematoma is the cause of a lowered consciousness in at least one-third of the patients in a poor clinical condition. This is most frequently the result of a ruptured middle cerebral artery aneurysm and urgent surgical evacuation is required, preferably with subsequent aneurysm repair.¹² Subdural hematomas are rare in SAH patients (less than 2%), but they can be life-threatening and should be treated as soon as possible.¹³

Table 1 | World Federation of Neurosurgical Societies (WFNS) SAH grading scale

Grade	GCS-score	Motor deficit
I	15	absent
II	14+13	absent
III	14+13	present
IV	12-7	present or absent
V	6-3	present of absent

GCS=Glasgow Coma Scale

Treatment modalities

Aneurysm repair can be performed via craniotomy with microsurgical clip obliteration ('clipping') or via an endovascular route using electrolytically detachable coils for occlusion ('coiling'). In 1991, Guglielmi was the first describing treatment with these coils and over the last decades, endovascular coiling is increasingly being used. Although endovascular

coiling avoids the need of a craniotomy, coiling is associated with an increased risk for incomplete occlusion and subsequent increased risk of rebleeding after treatment. In case of incomplete occlusion, additional coiling is indicated to achieve complete obligation. Therefore, a five-year follow-up is recommended after coiling. After clipping of the aneurysm, the chance of incomplete occlusion is negligible and thus long-term follow-up is superfluous.⁸

In 2002, the International Subarachnoid Aneurysm Trial (ISAT), a multicenter randomized trial, compared neurosurgical and endovascular repair in 2143 patients whom both treatment modalities were eligible.^{14,15} This study described a significantly better outcome (in death and dependency) after 1 year using endovascular coiling, although the risk of rebleeding after coiling was slightly higher compared to clipping. After five years of follow-up the benefit of coiling in terms of 'death and dependency' was vanished, but the benefit for death only was preserved over time. Therefore, coiling was still considered the treatment modality of choice.¹⁶

The results of the ISAT trial led to a significant change in treatment of aneurysmal SAH. Previously, the majority of the aneurysms were clipped, but nowadays most centers prefer coiling, with up to 80% of all aneurysms being coiled.¹⁷ Although ISAT aimed to include all patients seen in daily practice, the final included population did not fully cover this wide range of patients. Most of the patients were in a good clinical condition at time of randomization, and harbored small anterior aneurysms.¹⁴ In most neurovascular centers, the ISAT results were extrapolated towards all SAH patients, despite that for many subgroups the benefit of coiling was not well established such as for patients with middle cerebral artery aneurysms, in which clipping is often preferred because of the favorable approachability by craniotomy.⁸

Another major point of critic on the ISAT trial, was the inclusion of post-randomization pre-treatment deaths¹⁸, which occurred significantly more in the neurovascular treatment arm. In addition, a substantial difference in time to treatment was present, with the coiled patients treated earlier.^{14,15} There are concerns that due to this treatment delay the patients in the neurosurgical arm were more subject to pre-treatment rebleeding of the aneurysm, with major consequences for outcome after aSAH.^{18,19}

Rebleeding

Rebleeding of the aneurysm is an early complication after aSAH, with reported cumulative incidences of 8-23% in the first 72 hours after the ictus and a peak in the first 24 hours.²⁰ Early rebleeding is associated with high mortality rates and poor prognosis for clinical outcome among survivors, which makes it one of the most feared complications after aneurysmal SAH.

The exact mechanism behind rebleeding remains unknown. It has been associated with a sudden change in transmural pressure over the aneurysm wall, due to a change in mean arterial blood pressure or cerebrospinal fluid pressure. Furthermore, several studies investigated coagulation and fibrinolysis in relation to rebleeding, as systemic administration of antifibrinolytics such as tranexamic acid was shown to have a favorable effect on rebleeding rate.²⁰ Long-term treatment with antifibrinolytic agents to prevent rebleeding has been routinely used before, but when it appeared to increase the risk of infarctions, this was abandoned.²¹ Some studies advocated for short-term use of tranexamic acid to prevent ultra-early rebleeding, but it remains unclear whether this is actually improving overall outcome.^{22,23}

When the ruptured aneurysm is secured by either coiling or clipping, the chance of rebleeding in the acute phase is minimised.¹⁴ Both the European as the American guidelines recommend aneurysm repair as soon as feasible but at least within <72 hours after ictus, but there is no consensus about the optimal timing for aneurysm repair.^{8,24} In this timeframe, the patient is still at risk for early rebleeding of the ruptured aneurysm. It is not exactly known if some patients are more prone for rebleeding and should be treated faster compared to other patients. In the past, risk factors for rebleeding were only investigated in rather small series of patients and results are conflicting, so firm evidence regarding this is lacking.²⁰

Delayed cerebral ischemia

In patients surviving the first 72 hours after SAH, delayed cerebral ischemia (DCI) is a major cause of death and disability. It appears in approximately one-third of the survivors, however exact incidence rates are not well determined, mainly because there is no clear definition of DCI.^{8,25} Most often it is defined as a change in level of consciousness or new focal neurologic deficits, in combination with newly visible radiographic infarction. The exact underlying pathophysiological mechanisms of DCI remain obscure, but multifocal cerebral hypoperfusion is considered a final common pathway.^{26,27}

DCI is associated with narrowing of the angiographically visible cerebral arteries, also called vasospasm, although a causal relationship has never been proofed.⁸ Vasospasm is most frequently occurring at day 7-10 after the initial ictus and can be asymptomatic, but in 20-30% of the patients it can cause serious neurological symptoms.²⁸ It is difficult to predict which patients will develop ischemic deficits; some patients with significant artery narrowing in large vessels will never be symptomatic, whereas others with relatively modest spasms will be symptomatic and develop ischemia.

To date, there is no adequate treatment to prevent DCI, but some therapies are proven beneficial in reducing poor outcome. In all SAH patients, maintenance of euvolemia and normal cerebral blood flow is recommended to prevent ischemia. Furthermore, oral administration of nimodipine, a calcium channel blocker, seems to reduce the incidence of severe neurological deficits, and is therefore also recommended in all patients after aSAH.⁸ Traditionally, when the first signs of DCI appear, triple-H therapy (hemodilution hypervolemia, and hypertensive therapy) was given to improve cerebral blood flow. Accumulating literature, however, show no improvement in outcome, so triple-H therapy has shifted more towards euvolemia-induced hypertension.⁸ Several recent trials investigated the benefit of drugs such as statins, endothelial-1 receptor antagonists and magnesium, but none are proven beneficial.²⁹⁻³¹ Therefore, there is still no effective (preventive) treatment for patients with severe vasospasm and DCI.

Outcome after SAH

Due to improvements in diagnostic techniques and treatment modalities, nowadays more patients survive after a SAH.³² Among survivors, the functional outcome is affected by brain injury from the initial SAH and its subsequent complications and is highly heterogeneous between people. Approximately half of the survivors will remain significantly functionally impaired, are often dependent in daily activities and cannot return to their previous home or work. The other group will recover relatively well, most often with mild cognitive symptoms, such as problems with memory, concentration and mental fatigue.^{8,33}

In clinical practice, early and accurate prediction of the patients' outcome is essential for decision-making regarding timing of aneurysm repair and treatment of concomitant disorders. The initial neurological condition on admission has proven to be the strongest predictor for outcome and is therefore used for the development of several grading scales over the last decades.⁸ The first grading scale that became widely accepted was developed by Botterell et al. in 1956, and was followed by the Hunt and Hess scale in 1968, which is still in use by some institutions.^{34,35} As mentioned above, the WFNS grading scale, introduced in 1988, is nowadays regarded as the gold standard for initial clinical assessment. Nevertheless, there is room for improvement as 20% of the WFNS grade V patients recover without any important physical or cognitive deficits.³⁶ A more accurate initial prediction of outcome after SAH therefore remains a challenge.

The Groningen Subarachnoid Hemorrhage Cohort

The University Medical Center Groningen (UMCG) is one of the largest university hospitals of the Netherlands with 1300 beds. It is located in the north of the Netherlands, with a potential referral population of approximately 2.000.000 inhabitants. Vascular

neurosurgical care in the region is exclusively taken care by the UMCG since the early nineties. Since January 1998, a prospective data registration of all patients with non-traumatic subarachnoid hemorrhage admitted to the UMCG is instituted. Up to January 2017 (and still including), 1946 SAH patients have been included, both aneurysmal SAHs as non-aneurysmal SAHs. This SAH cohort is unique not only in its size, but also in the number of collected variables and the completeness of the data. Therefore, the Groningen Subarachnoid Hemorrhage Cohort forms a reliable source of information for clinically relevant research questions considering SAH patients.

Aim and outline of this thesis

Although case-fatality rates of patients with SAH has been decreased over the past decades due to improvements in diagnostics and treatment, mortality and morbidity rates remain high. Therefore, there is still room for improvements in treatment of SAH patients. Aim of this thesis was to broaden knowledge about aneurysm rupture, and to gain more insight in predictive factors for rebleeding and the patients' outcome after SAH. Therefore, we conducted the following studies, mainly using data of the Groningen Subarachnoid Hemorrhage Cohort.

As mentioned above, there is an on-going search for conditions that induce SAH. There are suggestions that a seasonal pattern of SAH exists, however, this is never indisputably confirmed, as is the relationship with the weather. In **chapter 2**, we therefore reviewed the Groningen Subarachnoid Hemorrhage Cohort on the seasonal incidence of SAH and the association between SAH and local meteorological factors.

After the occurrence of a SAH, rebleeding is one of the most feared complications, with reported mortality rates up to 60%. Exact incidence rates of rebleeding are not known, and there is little knowledge about risk factors for rebleeding. In **chapter 3**, we therefore assessed rebleeding rates in relation to time after aSAH, and identified risk factors for early rebleeding.

To prevent the patient from rebleeding of the aneurysm, aneurysm repair should be instigated soon after aSAH. The decision to treat the aneurysm and subsequent timing of the treatment is depending of the patients expected clinical outcome. The WFNS grading scale is currently considered the gold standard for predicting outcome, but the accuracy of the WFNS is subject of debate, as is the timing of the assessment. In **chapter 4**, we examined the optimal timing of assessment of the WFNS grade, either on admission or after neurological resuscitation. Furthermore, we determined other clinically relevant predictors for outcome. In **chapter 5**, we used these results to develop a new prediction

model for short-term outcome after SAH. For validation of this prediction model we used the cohort of the ISAT trial.

ISAT is the only substantial trial comparing the two treatment modalities, and showed that coiling was associated with better clinical outcomes. However, it is known that in ISAT, patients in the clipping arm were treated significantly later compared to the coiling arm. Also, more patients in the clipping arm died before treatment could be instigated. In **chapter 6**, we therefore investigated the impact of rebleeding and treatment delay on the outcomes of ISAT. Finally, in **chapter 7** the results of our studies as well as clinical implications and recommendations for future research are discussed.

REFERENCES

1. Feigin VL, Lawes CM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; 8:355-69.
2. de Rooij NK, Linn FH, van der Plas JA, et al. Incidence of subarachnoid hemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry* 2007; 78:1365-72.
3. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid hemorrhage. *Lancet Neurol* 2011; 10:349-356.
4. van Gijn J, Rinkel GJ. Subarachnoid hemorrhage: diagnosis, causes and management. *Brain* 2001; 124:249-78.
5. Rinkel GJ, van Gijn J, Wijdicks EF. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. *Stroke* 1993; 24:1403-9.
6. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid hemorrhage. *Lancet* 2007; 369:306-318.
7. Brown RD Jr, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. *Lancet Neurol* 2014; 13:393-404.
8. Connolly, ES Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; 43:1711-1737.
9. Linn FH, Rinkel GJ, Algra A, et al. Headache characteristics in subarachnoid hemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998; 65:791-3.
10. Teasdale GM, Drake CG, Hunt W, et al. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurosurgical Societies. *J Neurol, Neurosurg Psychiatry* 1988; 51:1457-60.
11. Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales: a systematic review. *Neurocrit Care* 2005; 2:110-8.
12. Niemann DB, Wills AD, Maartens NF, et al. Treatment of intracerebral hematomas caused by aneurysm rupture: coil placement followed by clot evacuation. *J Neurosurg* 2003; 99:843-7.
13. Inamasu J, Saito R, Nakamura Y, et al. Acute subdural hematoma caused by ruptured cerebral aneurysms: diagnostic and therapeutic pitfalls. *Resuscitation* 2002; 52:71-76.
14. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized trial. *Lancet* 2002; 360:1267-1274.
15. Molyneux A, Kerr RS, Yu LM, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized comparison of effects on survival, dependency, seizures, rebleeding, subgroups and aneurysm occlusion. *Lancet* 2005; 6736:809-17.
16. Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid hemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009; 8:427-33.
17. Gnanalingham KK, Apostolopoulos V, Barazi S et al. The impact of the international subarachnoid aneurysm trial (ISAT) on the management of aneurysmal subarachnoid hemorrhage in a neurosurgical unit in the UK. *Clin Neurol Neurosurg* 2006; 108: 117-23.
18. Bakker NA, Metzemaekers JDM, Groen RJM et al. International subarachnoid aneurysm trial 2009: Endovascular coiling of ruptured intracranial aneurysms has no significant advantage over neurosurgical clipping. *Neurosurgery* 2010; 66: 961-2.

19. Bakker NA, van Dijk JMC, Veeger NJGM. ISAT: End of the debate on coiling versus clipping? *Lancet* 2015; 385: 2250–1.
20. Larsen CC, Astrup J. Rebleeding after aneurysmal subarachnoid hemorrhage: a literature review. *World Neurosurg* 2013; 79:307–12.
21. Baharoglu MI, Germans MR, Rinkel GJ. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage. *Cochrane Database Syst Rev* 2013; 8:CD001245.
22. Hillman J, Fridriksson S, Nilsson O, et al. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg.* 2002; 97:771–8.
23. M.R. Harrigan, K.F. Rajneesh, A.A. Ardelt, et al. Short-term antifibrinolytic therapy before early aneurysm treatment in subarachnoid hemorrhage: effects on rehemorrhage, cerebral ischemia, and hydrocephalus. *Neurosurgery* 2010; 67:935–939
24. Steiner T, Juvela S, Unterberg A et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage. *Cerebrovasc Dis* 2013; 35:93–112.
25. Roos YB, de Haan RJ, Beenen LF, et al. Complications and outcome in patients with aneurysmal subarachnoid hemorrhage: A prospective hospital based cohort study in the Netherlands. *J Neurol Neurosurg Psychiatry* 2000; 68:337–341
26. Dankbaar JW, de Rooij NK, Smit EJ, et al. Changes in cerebral perfusion around the time of delayed cerebral ischemia in subarachnoid hemorrhage patients. *Cerebrovasc Dis* 2011; 32:133–140
27. Dankbaar JW, de Rooij NK, Velthuis BK, et al. Diagnosing delayed cerebral ischemia with different CT modalities in patients with subarachnoid hemorrhage with clinical deterioration. *Stroke* 2009; 40:3493–3498
28. Kassell NF, Sasaki T, Colohan AR, et al. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke.* 1985;16:562.
29. Kirkpatrick PJ, Turner CL, Smith C, et al. Simvastatin in aneurysmal subarachnoid hemorrhage (STASH): a multicenter randomized phase 3 trial. *Lancet Neurol* 2014; 13:666–75
30. Dorhout Mees SM, Algra A, Vandertop WP, et al. Magnesium for aneurysmal subarachnoid hemorrhage (MASH-2): a randomized placebo-controlled trial. *Lancet* 2012; 380: 44–49
31. Macdonald RL, Higashida RT, Keller E, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid hemorrhage undergoing surgical clipping: a randomized, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol* 2011; 10:618–25
32. Nieuwkamp DJ, Vaartjes I, Algra A, et al. Age- and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in The Netherlands. *Int J Stroke* 2013; 8:90–4
33. Buunk AM, Groen RJM, Wijbenga RA, et al. Mental versus physical fatigue after subarachnoid hemorrhage: differential associations with outcome. *Eur J Neurol.* 2018; 25:1313–e113.
34. Botterell EH, Loughheed WM, Scott JW, et al. Hypothermia, and interruption of carotid, or carotid and vertebral circulation, in the surgical management of intracranial aneurysms. *J Neurosurg* 1956; 13:1–42
35. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28:14–20
36. Haug T, Sorteberg A, Finset A, et al. Cognitive functioning and health-related quality of life 1 year after aneurysmal subarachnoid hemorrhage in preoperative comatose patients. *Neurosurgery* 2010; 66:475–84

Chapter 2.

Atmospheric pressure variation is a delayed trigger for aneurysmal subarachnoid hemorrhage

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ABSTRACT

Background

There is an on-going search for conditions that induce spontaneous subarachnoid hemorrhage (SAH). The seasonal pattern of SAH is shown in a large meta-analysis of the literature, but its explanation remains undecided. There is a need for sound meteorological data to further elucidate the seasonal influence on SAH. Because of the stable and densely monitored atmospheric situation in the north of the Netherlands, we reviewed our unique cohort on the seasonal incidence of SAH and the association between SAH and local atmospheric changes.

Methods

Our observational cohort study included 1535 patients with spontaneous SAH admitted to our neurovascular center in the north of the Netherlands between 2000 and 2015. Meteorological data could be linked to the day of the ictus. To compare SAH incidences over the year and to test the association with meteorological conditions, incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs) were used, calculated by Poisson regression analyses.

Results

Atmospheric pressure variations were significantly associated with aneurysmal SAH. In particular, the pressure change on the second and third day before the ictus was independently correlated to a higher incidence of aneurysmal SAH (IRR, 1.11; 95% CI - 1.00-1.23)). The IRR for aneurysmal SAH in July was calculated 0.67 (95% CI - 0.49-0.92) after adjustment for temperature and atmospheric pressure changes.

Conclusion

Atmospheric pressure variations are a delayed trigger for aneurysmal SAH. Also, a significantly decreased incidence of aneurysmal SAH was noted in July. The latter could not be explained by atmospheric pressure and temperature variations.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating type of stroke, although the case fatality is decreasing.¹ More knowledge on the pathophysiology and development of cerebral aneurysm is required, including risk factors contributing to the rupture of aneurysms. Currently, established risk factors for SAH are hypertension, alcohol excess and smoking.²

A seasonal pattern in incidence of SAH has been observed. Conflicting data have been published regarding the relation between temperature and incidence of SAH.^{1,3-13} Some studies found a relation between SAH and atmospheric pressure changes^{6,11,14-17}, while others could not.^{5,7-9,12,18} In a large meta-analysis of 72.694 patients no direct relation was found between occurrence of SAH and atmospheric pressure or temperature changes,¹⁹ which has led to the assumption that meteorological factors do not explain the seasonal occurrence of SAH. However, as mentioned by the authors, the review was based on very heterogeneous data from low-quality papers, due to small or heterogeneous cohorts or inaccurate weather data. Since the individual constituents of a meta-analysis define its overall quality,²⁰ this leads to results that are not generalizable.

Our SAH-referral region in the north of the Netherlands has no altitude differences and is located at sea level, which makes it homogeneous for atmospheric pressure and temperature. Also, detailed meteorological data is available from many automated weather stations in the referral area, allowing to link accurate meteorological measurements to an individual patient. This prompted us to perform a detailed review on the seasonal variation in SAH-incidence. In addition, we analyzed the association between SAH and temperature and atmospheric pressure. The unique combination of detailed SAH-patient information and local meteorological conditions at the time of the ictus distinguishes our study from previously reported studies.

METHODS

Patients

All consecutive patients with a spontaneous SAH referred to our academic neurovascular center in Groningen between January 2000 and December 2015 were included in this study. Over the years, clinically relevant data were collected in a prospectively kept database. SAH was confirmed with computed tomography (CT). Additional angiographic imaging (CT angiography and/or conventional angiography) was done to determine the presence of an aneurysm. Patients with SAH due to an arterial dissection were excluded, as well as pediatric patients. As such, a cohort of 1535 SAH-patients was eligible.

Meteorological data

All SAH patients in the north of the Netherlands (provinces Groningen, Friesland and Drenthe) are referred to the neurovascular unit of the University Medical Center Groningen. This district covers an area of 8992 square km with a temperate climate, harboring no differences in altitude. It is located at sea level. At the end of the study period, there were 1.718.390 inhabitants in this area according to the Central Bureau of Statistics in the Netherlands.

Quality-controlled meteorological data were retrieved from the weather station of the Royal Netherlands Meteorological Institute at Groningen Airport Eelde. Data from this station are typical for the entire study region. Meteorological data included mean atmospheric pressure, daily highest and lowest atmospheric pressure, mean temperature and daily maximum and minimum temperature. In the Netherlands, the seasons are winter (December-February); spring (March-May); summer (June-August); autumn (September-November).

Statistical analysis

Categorical data are presented as counts and percentages. Continuous variables are presented as mean with standard deviation or medians with interquartile ranges, depending on normality of data. Group differences are tested using chi-square tests or two sample unpaired t-tests. The day of onset of SAH is used to count the number of patients presenting with SAH for each day between 2000 and 2015. The incidences of SAH during months of the year were compared using incidence rate ratio (IRR) with corresponding 95% CIs, calculated by univariate Poisson regression analyses. Furthermore, univariate Poisson regression analyses were used to assess relationship between SAH and delta atmospheric pressure (maximum – minimum atmospheric pressure per day) and delta temperature (maximum – minimum temperature per day) at the day of SAH and one day, two days and three days before the ictus. Finally, month of the year, delta atmospheric pressure and delta temperature were combined in a multivariate Poisson regression analysis to test the independency of the variables. Prior to these analyses a log transformation on the delta atmospheric pressure and delta temperature was performed. All analyses were done for SAHs as a group and separately for the aneurysmal SAH and non-aneurysmal SAH. A p-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, USA).

RESULTS

In the cohort of 1535 patients, 62 percent of patients were female and mean age was 56 years. A symptomatic aneurysm was diagnosed in 1242 patients (table 1). The mean variation in daily atmospheric pressure over the year was 6.2 hPa; the mean difference in daily temperature over the year was 8.3 degrees Celsius.

Figure 1 shows the cumulated SAH-percentage, both aneurysmal and non-aneurysmal, per month over the period 2000-2015. Clearly, the lowest SAH percentage occurs in the month of July. When tested in the univariate Poisson regression analysis (table 2), the IRR of all SAH in July was calculated 0.68 (95% CI 0.53-0.89), due to a similar significant association in the subgroup of aneurysmal SAH (IRR 0.61, 95% CI 0.45-0.82). For non-aneurysmal SAH, there was no significant difference in incidence between the months of the year.

Figure 2a shows the total number of SAH per month, both aneurysmal and non-aneurysmal, plotted with the mean daily atmospheric pressure in the period 2000-2015. The IRRs for the association between SAH and change in atmospheric pressure are shown in table 3. A 1 hPa change in atmospheric pressure was significantly associated with an increased risk of SAH two days later (IRR 1.11, 95% CI 1.03-1.19). Also, a change of 1 hPa in the third day prior to the ictus, increases the risk of SAH (IRR 1.08, 95% CI 1.01-1.16). Combination of the second and the third day prior to SAH yielded the same significant association. Again, these results were only found in the subgroup of aneurysmal SAH. For non-aneurysmal SAH there was no significant association between change in atmospheric pressure and SAH.

Figure 2b shows the total number of SAH per month, both aneurysmal and non-aneurysmal, plotted with the mean daily temperature in the period 2000-2015. The IRRs for the association between SAH and change in temperature are shown in table 4. A change of 1 degree Celsius one day prior to the ictus, decreases the risk of SAH with an IRR of 0.89 (95% CI 0.82-0.98). The initial two days prior to the ictus combined yielded a similar significant association between change in temperature and SAH (IRR 0.86, 95% CI 0.77-0.97), which once more was due to the subgroup analysis of aneurysmal SAH. For non-aneurysmal SAH no significant association between change in temperature and bleeding was found.

Table 5 presents the result of the multivariate Poisson regression analysis. The IRR of aneurysmal SAH in July remains significantly lower when compared to other months (0.67, 95% CI 0.49-0.92). The variation in atmospheric pressure the second and third day prior to the ictus remained associated with higher incidence of aneurysmal SAH (IRR 1.11, 95% CI 1.00-1.23). This association was independent of the month of the year.

Table 1 | Baseline characteristics

Patient population	All SAH	Aneurysmal SAH		Non-aneurysmal SAH	p-value
Total (%)	1535 (100)	1242 (81)		293 (19)	
Female (%)	945 (62)	823 (66)		122 (41)	<0.001*
Mean age (SD)	56 (12.3)	56 (12.4)		57 (11.9)	0.16 †
History					
Hypertension (%)	344 (22)	302 (24)		42 (14)	<0.001*
Previous SAH (%)	29 (2)	28 (2)		1 (<1)	0.02*
Meteorological data	Mean (SD)	Median (IQR)		Minimum	Maximum
Pressure (hPa)	1014.8 (9.8)	1015.2 (1008.9-		964.2	1048.1
Delta pressure/day (hPa) ‡	6.2 (4.3)	1015.2)		0.7	42.9
Temperature (°C)	9.9 (6.3)	5.1 (3.1-8.2)		-19.5	35.4
Delta temp/day (°C) §	8.3 (3.8)	10.1 (5.5-14.8)		5.0	22.0
		7.9 (5.3-10.9)			
Frequency of SAH per day	0	1	2	3	4
Number of days	4517	1136	177	11	3

* Group differences were tested with the chi-square test. † Group differences were tested with the two sample unpaired t-test. ‡ Delta pressure=maximum – minimum atmospheric pressure at the day of SAH
§ Delta temperature=maximum – minimum temperature at the day of SAH

Table 2 | Poisson regression analysis examining the association between month of the year and the incidence of SAH. Coefficients are represented as incidence rate ratio's (IRRs).

	All SAH			Aneurysmal SAH			Non-aneurysmal SAH		
	IRR	95%CI	P-value	IRR	95%CI	P-value	IRR	95%CI	P-value
January	1.05	0.83-1.33	0.68	1.04	0.80-1.34	0.79	1.13	0.65-1.98	0.67
February	0.86	0.67-1.11	0.26	0.82	0.62-1.08	0.16	1.10	0.62-1.96	0.75
March	1.07	0.85-1.36	0.55	1.09	0.84-1.41	0.52	1.00	0.56-1.78	0.99
April	0.92	0.72-1.18	0.50	0.91	0.70-1.20	0.52	0.94	0.52-1.71	0.85
May	0.88	0.68-1.12	0.29	0.87	0.66-1.14	0.30	0.91	0.51-1.65	0.76
June	0.97	0.76-1.23	0.77	0.92	0.71-1.21	0.56	1.17	0.67-2.05	0.59
July	0.68	0.53-0.89	0.005	0.61	0.45-0.82	0.001	1.04	0.59-1.85	0.88
August	1.02	0.81-1.30	0.86	0.99	0.76-1.29	0.95	1.18	0.67-2.05	0.57
September	1.01	0.80-1.28	0.93	1.02	0.78-1.32	0.91	0.99	0.55-1.78	0.97
October	0.90	0.71-1.15	0.42	0.85	0.65-1.12	0.24	1.17	0.67-2.05	0.57
November	1.13	0.89-1.42	0.32	1.08	0.83-1.40	0.56	1.35	0.78-2.32	0.28
December	ref			ref			ref		

IRR = Incidence rate ratio's

Table 3 | Poisson regression analysis examining the association between the change in atmospheric pressure compared to previous days and the incidence of SAH.

	All SAH			Aneurysmal SAH			Non-aneurysmal SAH		
	IRR	95%CI	P-value	IRR	95%CI	P-value	IRR	95%CI	P-value
Delta P *	1.06	0.98-1.14	0.13	1.05	0.97-1.14	0.21	1.08	0.91-1.27	0.39
Delta P1†	1.02	0.95-1.10	0.56	1.02	0.94-1.10	0.73	1.05	0.89-1.25	0.55
Delta P2 ‡	1.11	1.03-1.19	0.006	1.13	1.04-1.22	0.004	1.03	0.87-1.22	0.74
Delta P3 §	1.08	1.01-1.16	0.04	1.10	1.01-1.19	0.03	1.02	0.86-1.21	0.80
Delta P23	1.11	1.02-1.21	0.01	1.13	1.03-1.25	0.009	1.03	0.85-1.24	0.80

IRR = Incidence rate ratio's * Delta P=maximum – minimum atmospheric pressure at the day of SAH

† P1 = one day before SAH ‡ P2 = two days before SAH § P3= three days before SAH || P23=day two and day three before SAH

Table 4 | Poisson regression analysis examining the association between the delta temperature and the incidence of SAH.

	All SAH			Aneurysmal SAH			Non-aneurysmal SAH		
	IRR	95%CI	P-value	IRR	95%CI	P-value	IRR	95%CI	P-value
Delta T*	0.94	0.86-1.03	0.21	0.95	0.86-1.06	0.38	0.89	0.72-1.10	0.30
Delta T1†	0.89	0.82-0.98	0.02	0.90	0.81-0.996	0.04	0.87	0.71-1.07	0.20
Delta T2‡	0.92	0.84-1.01	0.09	0.94	0.85-1.05	0.27	0.84	0.68-1.03	0.09
Delta T3§	1.00	0.92-1.11	0.87	0.99	0.89-1.10	0.81	1.10	0.89-1.38	0.38
Delta T12	0.86	0.77-0.97	0.02	0.88	0.77-1.00	0.06	0.80	0.61-1.05	0.11

IRR = Incidence rate ratio's * Delta T=maximum – minimum temperature at the day of SAH † T1 = one day

before SAH ‡ T2 = two days before SAH § T3= three days before SAH || T12=first two days before SAH

Table 5 | Multivariate Poisson regression analysis.

	All SAH			Aneurysmal SAH		
	IRR	95%CI	P-value	IRR	95%CI	P-value
Delta P23*	1.09	0.997-1.29	0.06	1.11	1.00-1.23	0.04
Delta T12†	0.89	0.76-1.03	0.12	0.92	0.78-1.09	0.33
Month						
January	1.04	0.82-1.32	0.75	1.02	0.79-1.33	0.87
February	0.87	0.68-1.12	0.30	0.82	0.62-1.09	0.18
March	1.13	0.89-1.43	0.33	1.13	0.87-1.47	0.35
April	1.01	0.78-1.32	0.95	0.99	0.74-1.32	0.95
May	0.97	0.74-1.26	0.82	0.95	0.71-1.27	0.71
June	1.07	0.83-1.39	0.59	1.01	0.76-1.36	0.92
July	0.76	0.57-1.00	0.05	0.67	0.49-0.92	0.01
August	1.14	0.89-1.47	0.31	1.10	0.83-1.45	0.53
September	1.10	0.86-1.42	0.45	1.10	0.83-1.45	0.51
October	0.96	0.74-1.23	0.72	0.89	0.67-1.18	0.41
November	1.14	0.90-1.44	0.28	1.09	0.84-1.41	0.51
December	ref	ref	ref	ref	ref	ref

IRR = Incidence rate ratio's * Delta P23=maximum – minimum atmospheric pressure at the day of SAH, at day two and day three before SAH

† Delta T12=maximum – minimum temperature at the day of SAH, at the first two days before SAH

Figure 1 | Total number of SAH, aneurysmal SAH and non-aneurysmal SAH in the period 2000-2015 depicted per month.

Figure 2a | Mean daily atmospheric pressure and total SAH in the period 2000-2015 depicted per month.

Figure 2b | Mean daily temperature and total SAH in the period 2000-2015 depicted per month.

DISCUSSION

In this large single-center study of 1535 SAH-patients, we found that a variation in atmospheric pressure provokes the occurrence of aneurysmal SAH two and three days later. This association was calculated independent of month of the year. Furthermore, we found that there are significantly less SAHs in July (which is mid-summer in our geographic area). None of these findings were consistent with non-aneurysmal SAH. The unique combined homogeneity of the study region and our detailed database adds to the existing literature on SAH and climate.

Atmospheric pressure and temperature

We found that a variation in atmospheric pressure significantly increases the risk on aneurysmal SAH two and three days later. Prior research demonstrated that decreased atmospheric pressure results in significant inhibition of interleukine-1-beta, an inflammatory factor which is a key mediator in aneurysm growth.^{29,30} We hypothesize that atmospheric pressure changes trigger the inflammation process in the aneurysm wall, which subsequently increases the risk of rupture two and three days after the exposure. Although speculative, another explanation is that atmospheric pressure has an effect on blood pressure and venous return, which increases the risk on SAH due to an augmented pressure on the aneurysm wall.^{14,17}

In our study, an independent association of change in temperature and incidence of SAH was not found, despite many other studies.^{5,7,9,12,18} Variation in temperature was associated with SAH in a univariate analysis, but combined with month of the year and atmospheric pressure it fell out. This suggests that temperature changes go along with atmospheric pressure changes. Hence, it is not temperature that influences the aneurysm, but rather atmospheric pressure. Nevertheless, it could be that the temperature variation in our region is too small. In Baltimore, steep changes in temperature might explain why there was an association of SAH and temperature in that area.⁸ Again, a possible effect of temperature has been explained by its effect on blood pressure. Low temperatures induce peripheral vasoconstriction leading to an increased blood pressure.^{9,31}

Month of the year

Consistent with our findings, many other authors reported a declined incidence of SAH in the summer.^{9,11,19,21-23} In our analysis, temperature and atmospheric pressure variation could not explain this seasonal difference. In the literature, some other suggestions have been put forward. Lai et al. suggested that the decrease of SAH in the summer might be mediated by an increased sunlight exposure.¹⁰ Subsequently, Guan et al. found higher

incidence of hypovitaminosis D in their cohort of treated cerebral aneurysms.²⁴ Vitamin D receptors play an important role in the expression of vascular endothelial growth factor, and enzymes that affect the development and remodeling of vessels, such as metalloproteinases. Vitamin D also has anti-proliferative effects on smooth muscle cells in the walls of arteries, in addition to potent anti-inflammatory effects.²⁵ Lack of vitamin D may induce an inflammatory process in the aneurysm wall that increases the risk of rupture. On the other hand, Feigin et al. reported an increase of aneurysmal SAH in winter on the Southern hemisphere and specifically a decrease in July, which is the month with the 2nd lowest monthly sunshine hours.²²

Another explanation of the seasonal pattern might be influenza activity.^{14,19} Influenza epidemics occur less in summer than in the other seasons. Also, Backes et al. showed in a large study an increased incidence of SAH during epidemic influenza, independent of temperature.⁴ Influenza is known to trigger multiple inflammatory factors, particularly tumor necrosis factor alpha, which is an important modulator in the formation and rupture of aneurysms.^{4,13,26,27}

Furthermore, a parameter that often has been studied in SAH is humidity. However, only few authors reported a relationship with the incidence of SAH. Hughes et al. found that humidity correlates with SAH incidence.⁹ It has been suggested that humid environments cause an expansion of plasma blood volume and therefore increase blood pressure and thus the risk of SAH.^{9,28}

It is important to note that the summer vacations often occur in July. It is however not likely that the catchment population in July will decrease significantly. First of all because The Netherlands have a spreading system for the school summer vacations. The dates of the vacation vary each year and are equally spread over July and August, depending of the country's region. Furthermore, the average age of the SAH patients is 56 years. In general, these people do not depend on the school vacations anymore since their children are older. Last, our northern region is a popular summer destination for the entire country, so the population might shift, but would not decrease significantly.

As suggested by Steenhuijsen et al. (2012) it would be interesting to have information about seasonal changes in blood pressure since hypertension is a well-known risk factor for SAH.^{2,19} It is possible that summertime may induce changes in behavior affecting arterial blood pressure and subsequently SAH.¹²

Comparison with other studies

Compared to other studies, there are some interesting remarks that may color the interpretation and generalizability of the previously performed studies. In our study, the actual day of the ictus was considered, while in other studies the exact day of the SAH was not known and the day of presentation in the hospital or the call of the ambulance was analyzed.^{3,4,7,8} It is known that ictus and presentation at the hospital can differ, especially in milder cases of SAH. In addition, in previously performed studies,^{4,9,10,18} the meteorological data per week or even per month were used, which makes it hard to determine a possible association. Since physiological changes due to weather changes occur in short time, increased incidence of rupture would be expected within days. Therefore, our use of detailed meteorological data of each day over the past 15 years, directly linked to the day of ictus of each patient, is superior. Furthermore, an important strength of our study is that it was conducted in a homogeneous area of both temperature and pressure. Also, our calculations were based on first hand data about the ictus (exact time and place) and the local meteorological details. In contrast, some other studies included SAH-patients with incorrect or unspecified meteorological data.^{8,32,12}

Limitations

Some limitations of our study also need to be addressed. First, our prospectively collected data were analyzed retrospectively. Furthermore, we were not able to link the possible confounders such as age, gender and hypertension to the Poisson regression analysis. Last, as in many other studies, deaths prior to presentation in the hospital were not included.

Conclusions

Atmospheric pressure variations are a delayed trigger for aneurysmal SAH. Also, a significantly decreased incidence of aneurysmal SAH was noted in the month of July. The latter could not be explained by atmospheric pressure and temperature variations.

REFERENCES

1. Nieuwkamp DJ, Vaartjes I, Algra A, et al. Age- and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the Netherlands. *Int J Stroke*. 2013;8:90–94
2. Feigin VL, Rinkel GJE, Lawes CMM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005; 36:2773–80
3. Abe T, Ohde S, Ishimatsu S, et al. Effects of meteorological factors on the onset of subarachnoid hemorrhage: a time-series analysis. *J Clin Neurosci*. 2008; 15:1005–10
4. Backes D, Rinkel GJE, Algra A, et al. Increased incidence of subarachnoid hemorrhage during cold temperatures and influenza epidemics. *J Neurosurg*. 2016; 125:1–9
5. Beseoglu K, Hänggi D, Stummer W, et al. Dependence of subarachnoid hemorrhage on climate conditions: a systematic meteorological analysis from the dusseldorf metropolitan area. *Neurosurgery*. 2008; 62:1033–8–9
6. Chyatte D, Chen TL, Bronstein K, et al. Seasonal fluctuation in the incidence of intracranial aneurysm rupture and its relationship to changing climatic conditions. *J Neurosurg*. 1994; 81:525–30
7. Cowperthwaite MC, Burnett MG. The association between weather and spontaneous subarachnoid hemorrhage: an analysis of 155 US hospitals. *Neurosurgery*. 2011; 68:132–8–9
8. Gill RS, Hambridge HL, Schneider EB, et al. Falling temperature and colder weather are associated with an increased risk of aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2013; 79:136–42
9. Hughes MA, Grover PJ, Butler CR, et al. A 5-year retrospective study assessing the association between seasonal and meteorological change and incidence of aneurysmal subarachnoid hemorrhage. *Br J Neurosurg*. 2010; 24:396–400
10. Lai PMR, Dasenbrock H, Du R. The association between meteorological parameters and aneurysmal subarachnoid hemorrhage: a nationwide analysis. *PLoS One*. 2014; 9:e112961
11. Lejeune JP, Vinchon M, Amouyel P, et al. Association of occurrence of aneurysmal bleeding with meteorologic variations in the north of France. *Stroke*. 1994; 25:338–41
12. Neidert MC, Sprenger M, Wernli H, et al. Meteorological influences on the incidence of aneurysmal subarachnoid hemorrhage - single center study of 511 patients. *PLoS One*. 2013; 8:e81621
13. Umemura K, Hirashima Y, Kurimoto M, et al. Involvement of meteorological factors and sex in the occurrence of subarachnoid hemorrhage in Japan. *Neurol Med Chir (Tokyo)* 2008; 48:101–7
14. Buxton N, Liu C, Dasic D, Moody P, et al. Relationship of aneurysmal subarachnoid hemorrhage to changes in atmospheric pressure: results of a prospective study. *J Neurosurg*. 2001; 95:391–2
15. Jehle D, Moscati R, Frye J, et al. The incidence of spontaneous subarachnoid hemorrhage with change in barometric pressure. *Am J Emerg Med*. 1994; 12:90–1

16. Landers AT, Narotam PK, Govender ST, et al. The effect of changes in barometric pressure on the risk of rupture of intracranial aneurysms. *Br J Neurosurg.* 1997; 11:191–5
17. Setzer M, Beck J, Hermann E, et al. The influence of barometric pressure changes and standard meteorological variables on the occurrence and clinical features of subarachnoid hemorrhage. *Surg Neurol.* 2007; 67:264–72
18. Oyoshi T, Nakayama M, Kuratsu J. Relationship between aneurysmal subarachnoid hemorrhage and climatic conditions in the subtropical region, Amami-Oshima, in Japan. *Neurol Med Chir (Tokyo).* 1999; 39:585–901
19. de Steenhuijsen Piters WAA, Algra A, van den Broek MFM, et al. Seasonal and meteorological determinants of aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurol.* 2013; 260:614–9
20. Liu W, Bakker NA, Groen RJM. What Ingredients Have You Used to Prepare This Delicious Lunch? A Critical Look Behind a Meta-analysis. *Ann Surg.* 2015; 262:e113–4
21. Arntz HR, Willich SN, Schreiber C, et al. Diurnal, weekly and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. *Eur Heart J.* 2000; 21:315–20
22. Feigin VL, Anderson CS, Anderson NE, et al. Is there a temporal pattern in the occurrence of subarachnoid hemorrhage in the southern hemisphere? Pooled data from 3 large, population-based incidence studies in Australasia, 1981 to 1997. *Stroke.* 2001; 32:613–9
23. Fischer T, Johnsen SP, Pedersen L, et al. Seasonal variation in hospitalization and case fatality of subarachnoid hemorrhage - a nationwide danish study on 9,367 patients. *Neuroepidemiology.* 2005; 24:32–7
24. Guan J, Karsy M, Eli I, et al. Increased Incidence of Hypovitaminosis D Among Patients Requiring Treatment for Cerebral Aneurysms. *World Neurosurg.* 2016; 88:15–20
25. Norman PE, Powell JT. Vitamin D, shedding light on the development of disease in peripheral arteries. *Arterioscler Thromb Vasc Biol.* 2005; 25:39–46
26. Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. *Stroke.* 2013; 44:3613–22
27. Starke RM, Raper DMS, Ding D, et al. Tumor necrosis factor- α modulates cerebral aneurysm formation and rupture. *Transl Stroke Res.* 2014; 5:269–77
28. Senay LC, Mitchell D, Wyndham CH. Acclimatization in a hot, humid environment: body fluid adjustments. *J Appl Physiol.* 1976; 40:786–96
29. Becker WJ, Cannon JG. Influence of barometric pressure on interleukin-1 beta secretion. *Am J Physiol Regul Integr Comp Physiol.* 2001; 280:1897–901.
30. Moriwaki T, Takagi Y, Sadamasa N, et al. Impaired progression of cerebral aneurysms in interleukin-1beta-deficient mice. *Stroke.* 2006; 37:900–5
31. Rønning P, Langmoen IA. Aneurysm rupture--does the weather matter? *World Neurosurg.* 2013; 79:62–3
32. Macdonald RL. Whether subarachnoid hemorrhage depends on the weather? *World Neurosurg.* 2013; 79:64–5

Chapter 3.

Predictive factors for rebleeding after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Background

One of the most feared complications after aneurysmal SAH is an early rebleeding before aneurysm repair. Predictors for such an often fatal rebleeding are largely unknown. We therefore aimed to determine predictors for an early rebleeding after aSAH in relation with time after ictus.

Methods

This observational prospective cohort study included all consecutive patients admitted with aSAH between January 1998 and December 2014 (n=1337) at our University Neurovascular Center. Clinical predictors for rebleeding ≤ 24 hours were identified using multivariable Cox regression analyses. Kaplan–Meier analyses were applied to evaluate the time of rebleeding ≤ 72 hours after aSAH.

Results

A modified Fisher grade of 3 to 4 was a predictor for an in-hospital rebleeding ≤ 24 hours after ictus (aHR 4.7; 95% CI 2.1–10.6). The numbers needed to treat to prevent 1 rebleeding ≤ 24 hours was calculated 15 (95% CI, 10–25). Also, the initiation of external cerebrospinal fluid drainage (aHR 1.9; 95% CI, 1.4–2.5) was independently associated with a rebleeding ≤ 24 hours. Cumulative in-hospital rebleeding rates were 5.8% ≤ 24 hours, and 1.2% in the time frame 24–72 hours after ictus.

Conclusion

In our opinion, timing of treatment of aSAH patients, especially those with a modified Fisher grade of 3 or 4 in a good clinical condition, should be reconsidered. These aSAH patients might be regarded a medical emergency, requiring aneurysm repair as soon as possible. In this respect, our findings should provoke the debate on timing of aneurysm repair, especially in patients considered to be at high risk for rebleeding.

INTRODUCTION

After an aneurysmal SAH, one of the most feared complications is an early rebleeding from the ruptured aneurysm with reported incidences of 8-23% in the first 72h after the ictus.¹ The consequences of rebleeding are severe, with reported mortality rates up to 60%.¹ Urgent repair of the ruptured aneurysm by endovascular coiling or neurosurgical clipping is thus of utmost importance; as soon as the aneurysm is successfully repaired, the chance of a rebleeding is negligible.²

In current clinical practice a swift and accurate diagnosis of aSAH is usually quickly established, but particularly its subsequent treatment is significantly delayed by several factors. Logistical issues, e.g. transfer time and availability of neurovascular centers, as well as the 24/7 treatment capacity within these dedicated centers may contribute to a treatment delay. Treatment of concomitant disorders, e.g. acute hydrocephalus requiring external cerebrospinal fluid (CSF) drainage, can also interfere with early treatment. Traditionally, the critical time-frame for ruptured aneurysm repair is set at <72 hours after ictus, unless the patient is in a moribund condition.^{3,4}

Recent studies have already extensively focused on the incidence of a rebleeding after aneurysm repair, especially related to the type of treatment.^{2,5} Although studies in the past have already showed that a rebleeding most frequently occurs in the first 24h after ictus,⁶⁻⁸ exact rebleeding rates in relation to time after ictus have never been undisputedly established.¹ Moreover, though several risk-factors have been linked to an early rebleeding in retrospective analyses of rather small series of patients,⁹⁻¹² firm evidence regarding risk-factors is lacking. In clinical practice, it is therefore still unknown which patients are at an increased risk for a rebleeding and thus require immediate aneurysm repair. In view of the aforementioned it was our aim to identify risk-factors for early rebleeding in relation to the exact time after ictus.

METHODS

Patients

Between January 1998 and December 2014, 1620 consecutive patients with a subarachnoid hemorrhage (SAH) were admitted to our university neurovascular center. All clinical relevant data of these patients were collected. Given the observational design of the study and the fact that treatment of patients was according to standard clinical care, our institutional review board decided, according to Dutch regulations, that informed consent was not required.

Treatment protocol

A standardized multidisciplinary protocol is applied to all SAH patients admitted to our center. Before 2002, SAH patients were subject to digital subtraction angiography <12 hours after admission. Since 2002, all patients undergo immediate computed tomography (CT) angiography after established diagnosis of SAH, followed by digital subtraction angiography <48 hours in case of a negative CT angiography. All imaging is immediately evaluated by an interventional neuroradiologist and a vascular neurosurgeon. If an underlying intracranial aneurysm is detected, treatment (either endovascular coiling or neurosurgical clipping) is instigated as soon as technically and logistically feasible, also dependent on the patients' clinical condition. In case of a concomitant space-occupying hematoma, emergency craniotomy with evacuation of the hematoma and concomitant clipping of the aneurysm is performed. Antifibrinolytic therapy has not been used during the study time frame.

Study inclusion

From the total of 1620 SAH patients, 1337 were aneurysmal, of whom 132 were excluded for this study: 101 patients with a fusiform or dissecting intracranial aneurysm, as well as 31 patients with a treated intracranial aneurysm in the past. As such, 1205 patients with a ruptured saccular intracranial aneurysm were considered eligible for this study (Figure 1).

Figure 1 | Flowchart of the included patients

Imaging

All available imaging of the included patients was re-analyzed by two reviewers (NAB and CED) to agree on the amount of blood on the initial CT-scan according to the modified Fisher (mFisher) scale¹³ (table 1) and maximum diameter of the aneurysm. In patients harboring multiple intracranial aneurysms in whom it was not possible to identify the symptomatic aneurysm (n=43), the aneurysm location was designated as 'unknown'. Imaging of patients admitted before 2000 was not available for re-evaluation. Although the radiological reports of these patients were available, mFisher grade and maximum aneurysm diameter were considered 'unknown', as they could not be reviewed again.

Table 1 | The modified Fisher (mFisher) scale

	Focal or diffuse thin SAH	Focal or diffuse thick SAH	IVH	
0	-	-	-	No subarachnoid blood; no intraventricular blood
1	+	-	-	Thin diffuse or focal subarachnoid blood; no intraventricular blood
2	+	-	+	Thin diffuse or local subarachnoid blood; with intraventricular blood
3	-	+	-	Thick focal or diffuse subarachnoid blood; no intraventricular blood
4	-	+	+	Thick local or diffuse subarachnoid blood; intraventricular blood

SAH=subarachnoid hemorrhage; IVH=intraventricular hematoma

Data analysis

The following data were prospectively collected: age at time of aSAH, sex, history of SAH, presence of hypertension (defined as a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg during multiple recent measurements or controlled using antihypertensive drugs), use of platelet inhibitors or vitamin-K antagonist, date and time of ictus, the World Federation of Neurosurgeons (WFNS) score¹⁴ on initial in-hospital assessment, type of bleeding pattern and amount of blood on the first CT-scan after aSAH, aneurysm location, size and type, the presence of hydrocephalus, the timing of placement of a ventricular or lumbar drainage system for external CSF drainage, type of aneurysm repair and time to aneurysm repair, rebleeding, and death because of any cause.

For this study, the location of the aneurysm was classified into: (1) the anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery), (2) the middle cerebral artery, (3) posterior communicating artery, (4) other internal carotid artery aneurysms, (5) the basilar artery, and (6) other arteries in the posterior circulation (including the vertebral artery, cerebellar arteries, and posterior

cerebral artery). Aneurysm size and age were both categorized into 5 consecutive groups, similar to the recent paper by Greving et al,¹⁵ whereas the amount of blood on the initial CT scan was classified according to the mFisher scale.

Outcome

The primary endpoint of this study was an in-hospital rebleeding ≤ 24 h after the ictus. Rebleedings up to 72h were also analyzed. A rebleeding of the ruptured intracranial aneurysm was defined as a sudden clinical deterioration with a concomitant increase of subarachnoid, intracerebral, or intraventricular blood on the subsequent CT-scan (performed <1 hour after onset of symptoms; $n=65$, 80%). A clinical deterioration was defined as a decrease in Glasgow Coma Scale (GCS) in awake patients. Patients in an already poor clinical condition are intubated and sedated and closely monitored on the intensive care unit (ICU) with the large majority already having an external ventricular catheter. In case of a sudden change of blood pressure, pupil size or fresh blood coming out the CSF-drainage system, a CT is performed to confirm a rebleeding. Patients who suddenly died without CT confirmation of a rebleeding ($n=16$, 20%) were classified as a rebleeding if similar signs and symptoms occurred and/or if the external CSF-drainage system produced fresh blood. The time of rebleeding after ictus was determined at time of onset of symptoms or by the time of the confirmatory CT-scan.

Statistical analysis

Events (rebleedings) ≤ 24 h were measured from time of ictus until time of rebleeding in hours. Patients without a rebleeding (controls) were censored at the time of aneurysm repair or at time of death due to any cause. One minus survival curves were depicted by the method of Kaplan-Meier. Log-rank tests were applied when deemed necessary. Categorical data are presented as counts and percentages. Continuous variables are presented as mean with SD or medians with interquartile ranges (IQR), depending on normality of data. Hazard ratios (HR) for a rebleeding were obtained using multivariable Cox proportional hazard survival analysis. After univariate analysis of all clinically relevant covariates, those with a p -value <0.15 were included in the initial multivariable model.¹⁶ A backward elimination strategy was used to achieve the most suitable model to estimate the adjusted hazard ratios (aHR) with the final multivariable model only including covariates associated with a rebleeding at a level of $p<0.10$. Numbers needed to treat (NNT) and 95% confidence intervals of patients with a high mFisher grade (3-4) to prevent one rebleeding ≤ 24 h with an ultra-early treatment strategy were calculated as the reciprocal of the absolute risk reduction. A rebleeding ≤ 3 h after ictus was considered non-preventable. A two-tailed p -value of 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS software (version 22.0, SPSS Inc.).

RESULTS

Baseline patient characteristics

Patient characteristics are shown in table 2. Of all patients, a female predominance was observed (67%), and median age was 55 years (IQR 46-64 years). A group of 374 patients (31%) was in a poor clinical condition (WFNS 4 or 5) at time of admission. Aneurysms of the anterior cerebral arteries followed by the middle cerebral artery were most frequently observed. A total of 286 patients (21%) required external CSF-drainage before aneurysm repair because of acute hydrocephalus $\leq$ 24h after the ictus.

Cumulative incidence of early rebleeding after aSAH and treatment

Rebleeding $\leq$ 24 hours was confirmed in 70/1205 patients (5.8%); an additional 11/906 patients (1.2%) had a rebleeding between 24 and 72 hours after the ictus; 299 patients had already been censored during the first 24h. Of all patients with a rebleeding, 46 patients (57%) died as a result of the rebleeding. The mortality attributed to a rebleeding was not associated with time of rebleeding after ictus (data not shown). The incidence of an early rebleeding in relation to the exact time after ictus is depicted in the Kaplan-Meier analyses as shown in figure 2a with censoring of cases at time of aneurysm repair or death due to any cause. Median time of aneurysm repair in all patients treated $<$ 72h after ictus (n=648) was 31h (IQR 21-47h).

Risk factors for a rebleeding $\leq$ 24 hours

After univariate Cox regression analysis, the following covariates were associated ($p < 0.15$) with a rebleeding $\leq$ 24h (table 3): hypertension, WFNS-score at admission, larger aneurysm size, presence of an intracerebral hematoma, a higher mFisher grade and external CSF-drainage before aneurysm repair. Because of the observed strong dichotomization between mFisher grade of 0-2 and 3-4, the mFisher scale was dichotomized accordingly for further analysis. After multivariable analysis, an mFisher grade of 3-4 was associated with the occurrence of an early rebleeding (aHR 4.7, 95%CI 2.1-10.6). Also, initiation of external CSF-drainage was significantly associated with a rebleeding (aHR 1.9, 95%CI 1.4-2.5). The rebleeding occurred with a median of 1h after initiation of CSF-drainage (IQR 0-2h). If the mFisher scale was not dichotomized but included as a categorical covariate in the initial multivariable model, it remained significantly associated with a rebleeding (data not shown). Overall, the size of the aneurysm in relation with the risk of a rebleeding $\leq$ 24h showed a trend, with a larger aneurysm being at a greater risk for a rebleeding, especially those with a diameter $\geq$ 20mm (aHR 4.4, 1.6-13.2).

The NNT using an ultra-early treatment strategy in patients with a high mFisher grade (n=583) to prevent one rebleeding ≤ 24 h was calculated 15 (95%CI 10-32). As the mortality rate of patients suffering from a rebleeding ≤ 24 h was 60%, the NNT to prevent one death was 25 (95%CI 15-75). The association between rebleeding and the mFisher grade is illustrated in figure 2b, in which the dichotomized mFisher scale in relation with the occurrence of a rebleeding as a function of time is graphically presented (log-rank test: $p < 0.001$).

Table 2 | Baseline patient characteristics

	All patients	rebleeding ≤24hours		no early rebleeding ≤24h	
	Number	Number	(%)	Number	(%)
Total	1205	70	(100)	1135	(100)
Female	808	49	(70)	759	(67)
Age					
<40 years	123	4	(6)	119	(10)
40-49 years	291	13	(19)	278	(24)
50-59 years	343	26	(37)	317	(29)
60-69 years	272	17	(24)	255	(22)
>70 years	176	10	(14)	166	(15)
History					
Hypertension	268	21	(30)	247	(22)
Platelet inhibitor	44	2	(3)	42	(4)
Vitamin-K antagonist	18	2	(3)	16	(1)
WFNS grade on admission					
1	538	17	(24)	521	(47)
2	264	11	(16)	253	(22)
3	29	1	(2)	28	(2)
4	205	19	(27)	186	(16)
5	169	22	(31)	147	(13)
Aneurysm location					
Anterior cerebral arteries	483	30	(42)	453	(41)
Middle cerebral artery	246	14	(20)	232	(20)
Posterior communicating artery	187	9	(13)	178	(16)
Internal carotid arteries	73	3	(4)	70	(6)
Basilar artery	91	6	(9)	85	(7)
Posterior circulation (other)	82	4	(6)	78	(7)
Unknown (multiple aneurysms)	43	4	(6)	39	(3)
Aneurysm size					
0-4.9 mm	221	9	(13)	212	(19)
5-6.9 mm	310	15	(21)	295	(26)
7-9.9 mm	230	14	(20)	216	(19)
10-19.9 mm	196	15	(21)	181	(16)
≥20 mm	31	6	(9)	25	(2)
Unknown	217	11	(16)	206	(18)
modified Fisher scale					
0	38	1	(2)	37	(3)
1	267	1	(2)	266	(23)
2	226	5	(7)	221	(19)
3	177	10	(14)	167	(15)
4	406	48	(68)	358	(32)
Unknown	91	5	(7)	86	(8)
Intracerebral hematoma	187	19	(27)	168	(15)
Subdural hematoma	19	2	(3)	17	(2)
External CSF-drainage*	286	22	(31)	264	(23)

WFNS=World Federation of Neurosurgeons Scale, CSF=cerebrospinal fluid. * performed ≤ 24 hours, before treatment

Figure 2a and b | Kaplan Meier one minus survival analyses of patients with a rebleeding <72 hours after ictus (a) and dichotomized according to the mFisher scale (grade 0-2 versus 3-4) (b)

Table 3 | Univariate and multivariable Cox regression analysis of rebleeding ≤ 24 h after ictus.

Predictor	HR	95% CI	p-value	aHR	95% CI	p-value
	Univariate Cox regression			Multivariable Cox regression		
Female	0.9	0.5-1.5	0.61			
Age			0.36			
<40 years	1.0					
40-49 years	1.4	0.4-4.2	0.59			
50-59 years	2.4	0.8-6.8	0.11			
60-69 years	1.9	0.6-5.7	0.25			
>70 years	1.7	0.5-5.5	0.36			
History						
Hypertension	1.5	0.9-2.5	0.13			
Platelet inhibitor	0.8	0.2-3.1	0.70			
Vitamin-K antagonist	1.9	0.5-7.6	0.38			
WFNS grade on admission			<0.001			
1	1.0					
2	1.3	0.6-2.8	0.46			
3	1.1	0.2-8.2	0.93			
4	3.1	1.6-6.0	0.001			
5	4.6	2.4-8.6	<0.001			
Aneurysm location*			0.96			
Anterior cerebral arteries	1.0					
Middle cerebral artery	1.0	0.5-1.8	0.87			
Posterior communicating artery	0.8	0.4-1.6	0.51			
Internal carotid arteries	0.7	0.2-2.2	0.49			
Basilar artery	1.1	0.5-2.6	0.86			
Posterior circulation (other)	0.8	0.3-2.2	0.63			
Aneurysm diameter*			0.02			0.07
0.0-4.9 mm	1.0			1.0		
5.0-6.9 mm	1.2	0.5-2.8	0.65	1.7	0.7-3.9	0.24
7.0-9.9 mm	1.5	0.7-3.5	0.32	1.7	0.7-4.1	0.22
10.0-19.9 mm	2.0	0.9-4.5	0.10	2.2	0.9-5.4	0.07
≥ 20.0 mm	5.2	1.9-14.6	0.02	4.4	1.6-13.2	0.007
Modified Fisher scale*			<0.001			
0	1.0					
1	0.1	0.0-2.2	0.17			
2	0.8	0.1-7.2	0.87			
3	2.2	0.3-17.4	0.45			
4	4.8	0.7-34.9	0.12			
Modified Fisher grade 3-4*	8.1	3.7-17.7	<0.001	4.7	2.1-10.6	<0.001
Intracerebral hematoma	2.2	1.3-3.8	0.003			
Subdural hematoma	2.0	0.5-7.9	0.35			
External CSF-drainage**	1.4	0.9-2.4	0.146	1.9	1.4-2.5	<0.001

HR=Hazard ratio, aHR=adjusted Hazard Ratio, CI=Confidence Interval, WFNS=World Federation of Neurosurgeons scale, CSF=cerebrospinal fluid drainage. *Missing data: aneurysm location 3.6%, aneurysm diameter 18.0%, mFisher scale 7.6% **performed ≤ 24 hours, before treatment

DISCUSSION

The present study revealed some novel issues regarding the first 24h after aSAH. First, most importantly, a high mFisher grade (3 or 4) on the initial CT-scan, i.e. thick SAH with or without blood in both lateral ventricles, was identified as a strong independent predictor for rebleeding ≤ 24 h. Second, initiation of external CSF-drainage, either lumbar or ventricular, was found independently associated with a rebleeding ≤ 24 h.

In our study an mFisher grade of 3 or 4 was by far the strongest risk factor associated with a rebleeding ≤ 24 h, also independent of the patient's clinical condition as assessed by the WFNS-score at admission. This is remarkable, as this observation illustrates that not only the clinical condition on admission (either measured by the Hunt and Hess¹⁷ or WFNS score) is predictive for a rebleeding, as suggested by others,^{1,10} but rather the amount of blood as measured by the mFisher scale. We speculate that the amount of blood is a surrogate marker of the defect size and stability of the ruptured aneurysm wall, irrespective of the patient's clinical condition.

Our results suggest that patients might also be at an increased risk of rebleeding in case of external CSF-drainage before aneurysm repair. This observation confirms previous reports in the literature already suggesting the association between external CSF-drainage and a rebleeding.¹⁸⁻²⁰ Although the majority of rebleedings occurred almost immediately after initiation of CSF-drainage, a causal relation is still difficult to prove. A rebleeding after initiation of CSF-drainage might be explained by the sudden change of the transluminal pressure over the already damaged and vulnerable aneurysm wall. This, in turn, interferes with the critically stable local anatomical situation after aSAH. In this respect it would also be of interest to know whether the amount of CSF-drainage also plays a role. Apart from larger aneurysm size,¹² additional risk-factors as identified in the past could not be confirmed.^{1,10,11} This is probably explained by the methodological design and small sample size of these previous studies.

Both the European Stroke Organization (ESO)²¹ and the American Stroke Association (ASA)⁴ have issued a guideline in which it is recommended that treatment of a ruptured intracranial aneurysm should be instigated as soon as logistically feasible to reduce the risk of a rebleeding, preferably < 72 h after the ictus. In clinical practice, interpretation of this recommendation is highly heterogeneous; some neurovascular centers treat aSAH-patients on an emergency basis, but a significant proportion of centers consider the treatment of a ruptured intracranial aneurysm a 'daylight job', both endovascularly as well as surgically. Some authors advocate the use of antifibrinolytic therapy in the timeframe

between ictus and aneurysm-repair to avoid a rebleeding.^{22,23} Although this seems to be the case, the incidence of delayed cerebral ischemia is also significantly increased. It is therefore unknown whether the application of antifibrinolytic therapy is really useful.²⁴

It is clear that emergency aneurysm repair avoids the possible use of antifibrinolytic therapy. Such an early treatment strategy was already advocated by Phillips et al., reporting that treatment of ruptured intracranial aneurysms ≤ 24 h was associated with improved clinical outcomes compared to delayed treatment.²⁵ The same conclusion was drawn by Wong et al. in their sub analysis of the Intravenous Magnesium after Aneurysmal Subarachnoid Hemorrhage trial²⁶ as well as by Sandstrom et al.²⁷ Oudshoorn et al. made a plea for a delayed treatment strategy, as outcome in their series did not depend on aneurysm repair ≤ 24 h instead of 24-72h.²⁸ Their study, however, was based on a retrospective chart review of a highly heterogeneous cohort. Moreover, the 24h cut-off point used in their study is questionable, as the large majority of rebleedings occurred much earlier.

Of interest, in a recently published large retrospective comparative cohort study (n=1224), Park et al. clearly showed that emergency treatment (median time from admission to start of aneurysm repair 3h) was not only associated with a significantly lower rebleeding rate, but also with an improved clinical outcome.²⁹

Strengths and limitations

Some limitations of our study need to be addressed. The analyses of our prospectively kept cohort were retrospectively performed. As a result, not all previously reported predictors for a rebleeding could be assessed. Although premorbid hypertension was assessed, hypertension on admission, especially elevated systolic blood pressure, was not included in our model. This might have influenced our results because this variable has been associated with a rebleeding in previous studies. Also, missing imaging at the re-evaluation of the mFisher scale and aneurysm size may theoretically have influenced our results. Though, from a clinical point of view, there is no reason to believe that cases with an unknown mFisher scale and/or aneurysm size differ in any other way from the fully observed data-set. Regarding the generalizability of our conclusions and recommendations a remark has to be made regarding non-densely populated areas and countries with fewer resources; in such areas it obviously will be very difficult to achieve an ultra-early treatment strategy as proposed. Finally, an underestimation of the incidence of an early rebleeding after aSAH is very likely, since unmistakably a group of patients may already have suffered from a rebleeding before admission. Also, theoretically, patients on the ICU in an already poor clinical condition might have suffered from a rebleeding

without clear signs of it as they are intubated and sedated. However, as the large majority of these patients also have an external ventricular catheter, it is unlikely that this has actually happened, as the CSF-drainage system would have produced fresh blood.

Conclusions

The timing of treatment of aSAH patients with an mFisher grade of 3 or 4, especially in a good clinical condition, should be reconsidered. These patients could be regarded a medical emergency, requiring aneurysm repair as soon as possible, preferably 24/7. In patients with aSAH and a low mFisher grade (0-2), treatment <72h still seems acceptable.

REFERENCES

1. Larsen CC. Rebleeding after aneurysmal subarachnoid hemorrhage: a literature review. *World Neurosurg.* 2013; 79:307-12.
2. Molyneux AJ, Birks J, Clarke A, et al. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18-year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet* 2015; 385:691-697.
3. Öhman J, Heiskanen O. Timing of operation for ruptured supratentorial aneurysms: a prospective randomized study. *J Neurosurg* 1989; 70:55-60.
4. Connolly, E S Rabinstein, Alejandro Carhuapoma, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke* 2012; 43:1711-1737.
5. Molyneux A, Kerr RSC, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005; 366:809-817.
6. Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. *Neurosurgery* 1983; 13:479-481.
7. Kassell NF, Torner JC. The International Cooperative Study on Timing of Aneurysm Surgery-an update. *Stroke* 1984; 15:566-570.
8. Inagawa T, Kamiya K, Ogasawara H, et al. Rebleeding of ruptured intracranial aneurysms in the acute stage. *Surg Neurol* 1987; 28:93-99.
9. Fujii Y, Takeuchi S, Sasaki O, et al. Ultra-early rebleeding in spontaneous subarachnoid hemorrhage. *J Neurosurg* 1996; 84:35-42.
10. Naidech AM, Janjua N, Kreiter KT, et al. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. *Arch Neurol* 2005; 62:410-6.
11. Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. *Stroke* 2001; 32:1176-80.
12. Boogaarts HD, van Lieshout JH, van Amerongen MJ, et al. Aneurysm diameter as a risk factor for pretreatment rebleeding: a meta-analysis. *J Neurosurg* 2015; 122: 921-928.
13. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery* 2006; 59:21-7
14. Teasdale GM, Drake CG, Hunt W, et al. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurosurgical Societies. *J Neurol. Neurosurg. Psychiatry* 1988; 51: 1457.
15. Greving JP, Wermer MJH, Brown Jr RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol.* 2014; 13:59-66.
16. Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. *BMJ.* 2009; 338:1373-1377.

17. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg.* 1968; 28:14-20.
18. Ruijs AC, Dirven CM, Algra A, et al. The risk of rebleeding after external lumbar drainage in patients with untreated ruptured cerebral aneurysms. *Acta Neurochir.* 2005; 147:1157-61.
19. Hasan D, Vermeulen M, Wijdevicks EF, et al. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke.* 1989; 20:747-53.
20. Paré L, Delfino R, Leblanc R. The relationship of ventricular drainage to aneurysmal rebleeding. *J Neurosurg.* 1992; 76:422-7.
21. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage. *Cerebrovasc Dis.* 2013; 35:93-112.
22. Hillman J, Fridriksson S, Nilsson O, et al. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg.* 2002; 97:771-8.
23. Harrigan MR, Rajneesh KF, Ardelt AA, et al. Short-term antifibrinolytic therapy before early aneurysm treatment in subarachnoid hemorrhage: effects on rehemorrhage, cerebral ischemia, and hydrocephalus. *Neurosurgery* 2010; 67:935-939
24. Baharoglu MI, Germans MR, Rinkel GJ, et al. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage. *Cochrane Database Syst Rev.* 2013; 8:CD001245.
25. Phillips TJ, Dowling RJ, Yan B, et al. Does Treatment of Ruptured Intracranial Aneurysms Within 24 Hours Improve Clinical Outcome? *Stroke.* 2011; 42:1936-1945.
26. Wong GK, Boet R, Ng SC, et al. Ultra-early (within 24 hours) aneurysm treatment after subarachnoid hemorrhage. *World Neurosurg.* 2012; 77:311-315.
27. Sandström N, Yan B, Dowling R, et al. Comparison of microsurgery and endovascular treatment on clinical outcome following poor-grade subarachnoid hemorrhage. *J Clin Neurosci.* 2013; 20:1213-1218.
28. Oudshoorn S, Rinkel GE, Molyneux A, et al. Aneurysm Treatment <24 Versus 24-72h After Subarachnoid Hemorrhage. *Neurocrit Care.* 2014; 21:4-13.
29. Park J, Woo H, Kang DH, et al. Formal protocol for emergency treatment of ruptured intracranial aneurysms to reduce in-hospital rebleeding and improve clinical outcomes. *J Neurosurg.* 2015; 122:383-391.

Chapter 4.

Prediction of outcome after aneurysmal subarachnoid hemorrhage: timing of clinical assessment

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ABSTRACT

Background

Currently, early prediction of outcome after spontaneous subarachnoid hemorrhage (SAH) lacks accuracy despite multiple studies addressing this issue. The clinical condition of the patient on admission as assessed using the World Federation of Neurosurgical Societies (WFNS) grading scale is currently considered the gold standard. However, the timing of the clinical assessment is subject to debate, as is the contribution of additional predictors. The aim of this study was to identify either the conventional WFNS grade on admission or the WFNS after neurological resuscitation (rWFNS) grade as the most accurate predictor of outcome after SAH.

Methods

This prospective observational cohort study included 1620 consecutive patients with SAH admitted between January 1998 and December 2014 at our university neurovascular center. The primary outcome measure was a poor modified Rankin Scale score at the 2-month follow-up. Clinical predictors were identified using multivariable logistic regression analyses. Area under the receiver operating characteristic curve (AUC) analysis was used to test discriminative performance of the final model. An AUC of >0.8 was regarded as indicative of a model with good prognostic value.

Results

Poor outcome (modified Rankin Scale Score 4–6) was observed in 25% of the patients. The rWFNS grade was a significantly stronger predictor than the WFNS grade assessed on admission to the hospital. The rWFNS grade was significantly associated with poor outcome and with increasing age, higher modified Fisher Scale grade, larger aneurysm size, and the presence of an intracerebral hematoma (OR 1.8, 95% CI 1.2–2.8). The final model had an AUC of 0.87 (95%CI 0.85–0.89), which indicates excellent prognostic value regarding the discrimination between poor and good outcome after SAH.

Conclusion

In clinical practice and future research, neurological assessment and grading of patients should be performed using the rWFNS for a more accurate prediction of outcome after aSAH.

INTRODUCTION

As a result of improved diagnostic techniques and treatment modalities, case fatality rates after SAH have decreased significantly over the past 3 decades.¹ However, the reported mortality rate for aneurysmal SAH remains significant (35%), and one-third of the patients remain functionally dependent, even in the long term.² In clinical practice, early and accurate prediction of patient outcomes is essential for decision-making (e.g., for the timing of aneurysm repair and the treatment of concomitant disorders). Nowadays, the initial neurological condition of the patient, measured by the WFNS grade, is the gold standard for prediction of outcome, but it is known to be overly pessimistic.³

The timing of clinical neurological assessment and subsequent grading of the patient are particularly subject to debate.⁴⁻⁷ Owing to the presence of acute hydrocephalus or a large intracerebral hematoma, initial grading of the patient may be significantly impaired. After emergency neurological resuscitation by CSF drainage and/or craniotomy to remove a clot, the clinical condition of the patient with SAH may improve dramatically, often with consequences for the subsequent treatment strategy.^{8,9}

In 2007, Ransom et al.⁷ reported that an improved clinical condition after CSF drainage is related to a better long-term outcome. In addition, Giraldo et al. demonstrated that the WFNS after neurological resuscitation (rWFNS) grade was to be considered a better predictor of outcome than the WFNS grade on admission.⁵ Nevertheless, the design and small sample size of these studies hampers the drawing of firm conclusions. Therefore, the aim of this study was to identify either the traditional WFNS grade assessed on admission or the rWFNS grade as the most accurate predictor of outcome after SAH.

METHODS

Patients and inclusion

Between January 1998 and December 2014, 1620 consecutive patients with a non-traumatic SAH were admitted to our university neurovascular center. All patients with SAH were considered eligible for this study: 1236 patients with saccular SAH, 101 fusiform or dissection aneurysm patients, and 283 patients with a (perimesencephalic) non-aneurysmal SAH. Clinically relevant data of these patients were collected prospectively.

Treatment protocol

A standardized multidisciplinary protocol was applied to all patients with SAH admitted to our center. Before 2002, patients with SAH were subject to emergency digital

subtraction angiography (DSA) within 12 hours after admission. From 2002 onward, all patients underwent immediate CT angiography (CTA), followed by DSA within 48 hours in the case of negative CTA results. All imaging studies were evaluated immediately by an interventional neuroradiologist and a vascular neurosurgeon. If an underlying aneurysm was detected, patients in good neurological condition on admission (WFNS Grade I, II, or III) were treated as soon as technically and logistically feasible by using endovascular coiling or neurosurgical clipping, preferably within 72 hours after the ictus. In the meantime, patients who required CSF drainage underwent external lumbar or ventricular catheterization. Patients in poor neurological condition on admission (WFNS Grade IV or V) were not immediately considered for aneurysm repair; instead, neurological resuscitation was instigated first. After placement of an external ventricular drain, patients were closely monitored on the intensive care unit. If their clinical condition improved, aneurysm repair was instigated. Patients with a space-occupying intracranial hematoma (e.g., due to a ruptured middle cerebral artery aneurysm) underwent immediate craniotomy, evacuation of the hematoma, and concomitant clipping of the aneurysm regardless of their clinical condition (unless they were moribund). These neurological resuscitation procedures were performed in the first 24 hours after the initial SAH. After the resuscitation, the best neurological score in the first 12 hours after the intervention was considered the rWFNS grade. All patients who survived the initial treatment period visited our outpatient clinic 6 weeks (± 1 week) after discharge, if their clinical condition permitted. If their clinical condition did not permit them, information on their condition was obtained from their rehabilitation clinic or nursing home. Because a large majority of the patients had a hospital stay of approximately 3 weeks (end of vasospasm period), first-time follow-up was available 9 weeks (± 1 week) after ictus.

Imaging

All available images of the included patients were re-analyzed by 2 reviewers (CED and NAB) to reach agreement on the amount of blood shown on the initial CT scan according to the modified Fisher (mFisher) grade¹⁰ and the maximum diameter of the aneurysm. Imaging of the patients admitted before 2000 was not available for re-evaluation. Although the radiological reports of these patients were available, their mFisher grade and maximum aneurysm diameter were considered unknown for this study. When it was not possible to identify the symptomatic aneurysm because the patient died before CTA or DSA could be performed ($n=21$, all patients at Grade V), the aneurysm location was designated unknown.

Data analysis

The following data were collected prospectively: date of ictus; age at time of SAH; sex; history of SAH; presence of hypertension; use of a platelet inhibitor or a vitamin K antagonist; the WFNS grade on initial in-hospital assessment; the rWFNS grade; symptomatic aneurysm size, morphology, and location; amount of blood on the initial CT scan; presence of acute hydrocephalus that required initiation of CSF drainage within 24 hours after ictus; type and time of aneurysm repair; and early rebleeding. If it was not possible to identify the symptomatic aneurysm because of multiple aneurysms ($n=22$), the largest aneurysm was selected for analysis. When a patient died before CTA or DSA could be performed ($n=21$), the aneurysm was considered in the analysis to be of aneurysmal origin with unknown location and size. Hypertension was defined as systolic blood pressure of > 140 mm Hg or diastolic blood pressure of > 90 mm Hg during recent measurements or controlled using antihypertensive drugs. Age of the patient and the location and size of the symptomatic aneurysm were classified according to the recently published PHASES study.¹¹ The amount of blood was classified according to the mFisher Scale. Aneurysm morphology was categorized as 1) saccular, 2) fusiform, 3) intracranial artery dissection, or, in the case of a non-aneurysmal SAH, 5) non-aneurysmal or perimesencephalic. A rebleeding of the ruptured aneurysm was defined as a sudden clinical deterioration with a concomitant increase of subarachnoid, intracerebral, or intraventricular blood shown on the subsequent CT scan or when similar signs and symptoms occurred without CT confirmation.

Outcome measure

The primary outcome measure was poor functional outcome 2 months after the SAH according to the modified Rankin Scale (mRS) score,¹² as assessed by the treating vascular neurosurgeon at follow-up outpatient clinic contacts. A poor functional outcome was defined as an mRS score of 4–6.

Statistical analysis

The data were complete for all covariates except for aneurysm size (13% missing), mFisher grade (9% missing), and aneurysm location (1% missing). For these missing covariate data, multiple imputation (15 data sets) was performed with the linear regression method (multivariable analyses). Categorical data are presented as numbers and percentages, and continuous variables are presented as means with SD or medians with interquartile ranges (IQR), depending on normality of the data. The association between the WFNS and rWFNS grades and poor outcome was evaluated using binary logistic regression analysis. After univariate analyses, all clinically relevant covariates with a p value of <0.15 were entered in the initial multivariable model.¹³ A backward stepwise elimination strategy was applied to estimate the odds ratios (OR) with a cut-off point of <0.10 for inclusion in the final model.

Results are presented as ORs with corresponding 95% confidence intervals (CI). Sensitivity analysis was performed by multivariable logistic regression analysis excluding patients for whom data were missing (complete case analysis). As treatment of SAH patients has significantly changed over the years, additional sensitivity analyses were performed within 3 consecutive time frames (1998–2003, 2004–2009, and 2010–2014). The discriminative performance of the final model was calculated by a pooled area under the receiver operating characteristic curve (AUC) with a corresponding 95% CI. An AUC of >0.8 was regarded to indicate a model with good prognostic value. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 22.0).

RESULTS

Baseline patient characteristics are shown in table 1. A majority (62%) of the patients was female, and the median age was 55 years (IQR 46–65 years). In 1247 (78%) patients, a symptomatic aneurysm or multiple aneurysms were detected, whereas SAH was considered perimesencephalic or non-aneurysmal in 283 (17%) patients. In patients with a symptomatic aneurysm, the anterior cerebral artery was involved most frequently (33%), followed by the middle cerebral artery (18%). In 198 (12%) patients, a space-occupying intracranial hematoma was present. Hydrocephalus that required acute CSF drainage (within 24 hours after ictus) was present in 362 (22%) patients. Aneurysm repair was performed in 79% of the patients with aneurysmal SAH. In 38 patients, acute craniotomy for the evacuation of a space-occupying intracranial hematoma was performed. After neurological resuscitation, 106 (27%) of the 400 patients were in improved neurological condition after the intervention.

Baseline patient characteristics in the 3 consecutive timeframes (1998–2003, 2004–2009 and 2010–2014) are shown in supplemental table I (at the end of this chapter). In recent years, the age of the patients had increased, as has the number of patients at WFNS grade V on admission. Also, a change in the type of treatment was observed, with patients increasingly being treated endovascularly.

Two months after the initial SAH, 52 (3.2%) of the 1620 patients were lost to follow-up. Of the remaining 1568 patients, 394 (25%) had a poor outcome (mRS score 4–6), and the mortality rate was 17% (table 2). The percentage of patients with a poor outcome was higher at rWFNS Grade V than at WFNS Grade V (74% vs 67%, respectively; $p<0.001$, Chi-Square test). Throughout the different time frames, outcomes remained the same despite the observed increasing age and percentage of patients at WFNS Grade V on admission (supplemental table II).

Table 3 shows the logistic regression analysis results. After univariate analysis, both the WFNS and rWFNS grades were associated with poor functional outcome after 2 months. After adjustment for other significant variables in the univariate analysis, the rWFNS grade remained an independent predictor, whereas the WFNS was no longer significantly associated with poor outcome. When the rWFNS grade was excluded from the multivariable analysis, the WFNS remained significantly associated with poor outcome (data not shown). Other independent predictors of poor outcome were higher age, larger aneurysm size, a higher mFisher grade, and the presence of an intracerebral hematoma (OR 1.8, 95% CI 1.2–2.8). No significant difference in outcome was observed between patients treated endovascularly and those treated by neurosurgical clipping (OR 0.9, 95% CI 0.6–1.2). Sensitivity analyses for outcome after 2 months with complete case analysis, as well as the analyses within the three different timeframes showed essentially the same results (data not shown).

Regarding discriminative value, the predictive model derived from the multivariable logistic regression analysis resulted in a pooled AUC of 0.87 (95% CI 0.85–0.89; figure 1).

Table 1 | Baseline patient characteristics

Characteristic	Number (%)
Total no.	1620 (100)
Time frame	
1998–2003	462 (29)
2004–2009	635 (39)
2010–2014	523 (32)
Female	1001 (62)
Median age in years (IQR)	55 (46–65)
Age	
< 40 yrs.	159 (10)
40–49 yrs.	398 (25)
50–59 yrs.	458 (27)
60–69 yrs.	370 (23)
> 70 yrs.	235 (15)
History	
Previous SAH	31 (2)
Hypertension	336 (21)
Vitamin K antagonist	29 (2)
Platelet inhibitor	68 (4)
Initial WFNS grade	
I	848 (53)
II	313 (19)
III	34 (2)
IV	230 (14)
V	195 (12)

Table 1 | Continued

Characteristic	Number (%)
rWFNS grade	
I	872 (54)
II	332 (21)
III	38 (2)
IV	218 (13)
V	160 (10)
SAH type	
Aneurysm	1247 (78)
Saccular	1215
Fusiform aneurysm	32
Intracranial artery dissection	69 (4)
Perimesencephalic/non-aneurysmal	283 (17)
Unknown	21 (1)
Aneurysm location	
Anterior cerebral artery	514 (33)
Middle cerebral artery	288 (18)
Posterior communicating artery	202 (12)
Internal carotid artery	69 (4)
Posterior circulation artery	243 (15)
Perimesencephalic/non-aneurysmal	283 (17)
Unknown	21 (1)
Aneurysm size	
0–4.9 mm	227 (14)
5–6.9 mm	310 (20)
7–9.9 mm	249 (15)
10–19.9 mm	205 (13)
≥20 mm	30 (2)
Fusiform/intracranial dissection	101 (6)
Perimesencephalic/non-aneurysmal	283 (17)
Unknown	215 (13)
mFisher grade	
0	162 (10)
1	373 (23)
2	286 (18)
3	190 (12)
4	465 (29)
Unknown	144 (9)
Intracerebral hematoma	198 (12)
Subdural hematoma	20 (1)
Hydrocephalus that required CSF drainage*	362 (22)
Acute craniotomy	38 (2)
Early rebleeding (< 72 hr.)	81 (5)
Type of treatment	
Endovascular	562 (35)
Neurosurgical	497 (31)
No treatment	277 (17)
Perimesencephalic/non-aneurysmal	283 (17)

IQR=Interquartile range; SAH=subarachnoid hemorrhage; WFNS=World Federation of Neurosurgeons Societies SAH grading scale.

* External CSF drainage ≤ 24 hours after ictus and before treatment.

Table 2 | Distribution of functional outcome 2 months after SAH according to mRS score

Functional outcome (n=1568)	mRS Score	No. (%)
Good	0	406 (26)
	1	451 (29)
	2	195 (12)
	3	122 (8)
	Total	1174 (75)
Poor	4	110 (7)
	5	22 (1)
	6	262 (17)
	Total	394 (25)

SAH= subarachnoid hemorrhage; mRS=modified Ranking Scale

Table 3 | Results of univariate and multivariable logistic regression analyses for poor outcome 2 months after SAH

Covariates (n=1620)	Univariate Analysis			Multivariable Analysis†		
	OR	95% CI	p-value*	aOR	95% CI	p-value*
Age			< 0.001			< 0.001
< 40 years	1.0			1.0		
40–49 years	1.3	0.8–2.1	0.34	1.0	0.5–1.9	0.99
50–59 years	1.5	0.9–2.5	0.09	1.3	0.7–2.3	0.47
60–69 years	1.9	1.2–3.1	0.01	1.6	0.9–3.0	0.14
> 70 years	4.7	2.8–7.7	< 0.001	4.1	2.1–7.8	< 0.001
Male	0.9	0.7–1.1	0.40			
History						
Previous SAH	1.9	0.9–4.0	0.08			
Hypertension	1.4	1.1–1.9	0.07			
Vitamin K antagonist	1.1	0.5–2.6	0.76			
Platelet inhibitor	1.8	1.1–3.0	0.03			
WFNS grade			< 0.001			
I	1.0					
II	2.9	2.0–4.3	< 0.001			
III	6.5	3.1–13.9	< 0.001			
IV	12.6	8.8–18.2	< 0.001			
V	21.5	14.6–31.7	< 0.001			
rWFNS grade			< 0.001			< 0.001
I	1.0			1.0		
II	3.1	2.2–4.5	< 0.001	1.6	1.1–2.5	0.02
III	6.7	3.3–13.6	< 0.001	3.2	1.4–7.4	0.005
IV	12.6	8.8–18.0	< 0.001	5.7	3.7–8.8	< 0.001
V	29.3	19.1–44.8	< 0.001	12.1	7.3–19.9	< 0.001
Type of SAH			< 0.001			
Perimesencephalic/non-aneurysmal	1.0					
Aneurysmal (saccular/fusiform)	5.8	3.5–9.4	< 0.001			
Intracranial artery dissection	4.5	2.1–9.3	< 0.001			

Table 3 | Continued

Covariates (n=1620)	Univariate Analysis		Multivariable Analysis†		
	OR	95% CI	p-value*	aOR	95% CI
Aneurysm location			< 0.001		
Perimesencephalic/non-aneurysmal	1.0				
Anterior cerebral artery	3.5	2.0-6.3	< 0.001		
Middle cerebral artery	3.5	1.9-6.5	< 0.001		
Posterior communicating artery	4.4	2.4-8.2	< 0.001		
Internal carotid artery	2.8	1.3-6.1	0.009		
Posterior circulation artery	3.9	2.1-7.2	< 0.001		
Aneurysm size			< 0.001		
Perimesencephalic/non-aneurysmal	1.0			1.0	
0-4.9 mm	5.0	2.6-8.0	< 0.001	2.1	1.1-4.2
5-6.9 mm	4.0	2.3-6.7	< 0.001	1.8	0.9-3.6
7-9.9 mm	4.8	2.8-8.4	< 0.001	1.9	0.9-3.8
10-19.9 mm	8.1	4.8-14.0	< 0.001	3.4	1.7-6.7
≥ 20 mm	37.7	14.8-95.6	< 0.001	18.9	6.1-58.3
Non-saccular	4.0	2.1-7.9	< 0.001	2.6	1.1-6.0
mFisher grade			< 0.001		
0	1.0			1.0	
1	1.2	0.6-2.6	0.64	0.8	0.3-1.9
2	2.3	1.1-4.9	0.03	1.1	0.4-2.7
3	5.5	2.6-11.8	< 0.001	1.6	0.6-4.3
4	17.4	8.7-34.5	< 0.001	4.1	1.7-9.8
Intracerebral hematoma	3.7	2.7-5.1	< 0.001	1.8	1.2-2.8
Subdural hematoma	3.7	1.5-9.0	0.004		
Hydrocephalus, required CSF drainage‡	3.6	3.4-3.8	< 0.001		
Type of treatment (coiling vs clipping)	0.9	0.6-1.2	0.36		

aOR = adjusted OR; SAH= subarachnoid hemorrhage; WFNS= World Federation of Neurosurgeons Societies SAH grading scale. * Derived from Likelihood tests

† Effect estimates from the multivariable regression are adjusted for all other variables in the model ‡ Drainage ≤ 24h after ictus and before treatment

Figure 1 | Receiver operating characteristic (ROC) graph representing the discriminative value of the final pooled prediction model

DISCUSSION

In this study, we found that for the most accurate prediction of outcome after SAH, clinical assessment should be performed after neurological resuscitation. Other predictors in our final model were age, aneurysm size, amount of blood on the initial CT scan, and the presence of an intracranial hematoma.

The rWFNS grade determined in the clinical assessment was identified as the strongest predictor of outcome. The superiority of the rWFNS over the WFNS grade on admission is rather easy to understand; after “resuscitation” of the patients by CSF drainage or acute craniotomy, only the patients at a truly poor grade remain in this category. The negative predictive values of a space-occupying intracerebral hematoma, age, aneurysm size, and amount of blood on the initial CT scan have been documented before in rather small series but have not always been adjusted for all covariates.^{14,15}

Because the amount of subarachnoid blood on the initial CT scan as graded by the mFisher is an independent predictor, among others, the severity of SAH is not represented by the neurological condition alone. Besides the association between mFisher grade and poor outcome because of the increased incidence of delayed cerebral ischemia,¹⁰ the higher incidence of rebleeding in patients at mFisher Grade 3 or 4 also might add to the increased risk.¹⁶

In our study population, the percentage of patients with poor outcome may be considered relatively low because of the inclusion of patients with perimesencephalic SAH.² Also, in the 1990s, patients with SAH in very poor clinical condition were not always immediately referred to our hospital, leading to an underestimation of the true mortality rate, especially in time frame 1. At first glance, it seemed that outcomes after SAH did not improve during the subsequent time frames. However, over the years we find an increasing number of patients in poor neurological condition who were actively being treated, resulting in a significantly larger proportion of patients at WFNS Grade V in the last 2 time frames. In addition, although the patients were older over the past few years, outcomes remained the same, which reflects the advances made at our center in the management of patients with SAH.

Recently, Sano et al. made a plea for revision of the original WFNS grading scale.¹⁷ Their proposed modified WFNS removed the neurological deficit from the scale and instead discriminated between Glasgow Coma Scale scores 13 and 14. This change was supposed to lead to an overall stronger prediction value for outcome, which would especially result in better discrimination between Grades II and III as they pertain to outcome. Unfortunately, in their study, the differences in outcome between Grades III and IV now failed to be significant resulting in less accurate discrimination between low-grade and high-grade WFNS patients. In addition, as already noted by Wang and Heros,¹⁸ the presence of serious focal neurological deficits is unquestionably important for clinical outcome, and this was confirmed by our study; patients at WFNS Grade III had a twice-as-high risk of poor outcome than those at WFNS Grade II. In addition, when the rWFNS grade was omitted from the multivariable analysis, the WFNS grade emerged as most important predictor in the final model, with gradually ascending odds ratios for each individual grade. In this respect, we agree with Wang and Heros and argue for the use of the original WFNS scale, but only with the assessment of clinical condition after resuscitation.

Strengths and limitations

An important strength of this study is the accuracy of the model in predicting outcome, because the discriminative value of our model is substantially higher than that of previous models.¹⁹ Furthermore, the model was based on a large and representative group of all types of patients with spontaneous SAH, and only a minimal percentage of patients were lost to follow-up.

Some limitations of our study also need to be addressed. First, our cohort was analyzed retrospectively. Therefore, covariates that have been linked to outcome (e.g., laboratory parameters) could not be analyzed. However, we aimed to identify early determinable predictors, for development of a “bedside” prediction model. Second, although the use

of multiple imputation might be considered a weakness, imputing data is a validated and nowadays frequently used method for accounting for missing data.²⁰ Last, in patients who underwent immediate craniotomy for the evacuation of a space-occupying hematoma, the aneurysm was invariably treated concomitantly. In such cases, the prognostic value of the rWFNS grade regarding decision making might be considered of less value, because the rWFNS grade was assessed after aneurysm repair and treatment has already been performed. However, in other neurovascular centers, aneurysm repair is not necessarily performed during surgical evacuation of the hematoma but, rather, endovascularly after improvement of the clinical condition of the patient. In these cases, the rWFNS grade is still of contributing value in the decision-making process.

Clinical implications

This study demonstrated that the clinical condition of the patient after neurological resuscitation is more representative for the eventual outcome compared to the initial clinical condition on admission. Besides the rWFNS, four other, easily obtainable predictors for outcome after SAH were identified, resulting in a 'bedside' prediction model for outcome. Despite the excellent discriminative performance of the model, it is only validated in this single-center observational cohort. For generalizable results and clinical use in other neurovascular centers, this model needs to be validated, preferably using a cohort from a different center.^{11,21}

Conclusions

Clinical assessment should be performed after neurological resuscitation for the most accurate prediction of outcome. The rWFNS grade should be used in clinical practice and further research, which might significantly aid decision making at the early stage and provide more accurate information for patients and their relatives.

REFERENCES

1. Nieuwkamp DJ, Vaartjes I, Algra A, et al. Age- and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the netherlands. *Int J Stroke* 2013; 8:90-4
2. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid hemorrhage. *Lancet Neurol* 2011; 10:349-356
3. Haug T, Sorteberg A, Finset A, et al. Cognitive functioning and health-related quality of life 1 year after aneurysmal subarachnoid hemorrhage in preoperative comatose patients. *Neurosurgery* 2010; 66:475-84
4. Chiang VL, Claus EB, Awad IA. Toward more rational prediction of outcome in patients with high-grade subarachnoid hemorrhage. *Neurosurgery* 2000; 46:28-35
5. Giraldo EA, Mandrekar JN, Rubin MN, et al. Timing of clinical grade assessment and poor outcome in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2012; 117:15-9
6. Pegoli M, Mandrekar J, Rabinstein AA, et al. Predictors of excellent functional outcome in aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2015; 122:414-8
7. Ransom ER, Mocco J, Komotar RJ, et al. External ventricular drainage response in poor grade aneurysmal subarachnoid hemorrhage: Effect on preoperative grading and prognosis. *Neurocrit Care* 2007; 6:174-80
8. Hasan D, Vermeulen M, Wijdicks EF, et al. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke* 1989; 20:747-53
9. Milhorat TH. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 1987; 20:15-20
10. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modified fisher scale. *Neurosurgery* 2006; 59:21-27
11. Greving JP, Wermer MJH, Brown Jr RD, et al: Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: A pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; 13:59-66
12. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19:604-7
13. Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. *BMJ*. 2009; 338:1373-1377.
14. Brouwers PJ, Dippel DW, Vermeulen M, et al. Amount of blood on computed tomography as an independent predictor after aneurysm rupture. *Stroke* 1993; 24:809-814
15. Hauerberg J, Eskesen V, Rosenørn J. The prognostic significance of intracerebral hematoma as shown on CT scanning after aneurysmal subarachnoid hemorrhage. *Br J Neurosurg* 1994; 8:333-9
16. van Donkelaar CE, Bakker NA, Veeger NJ, et al. Predictive factors for rebleeding after aneurysmal subarachnoid hemorrhage: Rebleeding aneurysmal subarachnoid hemorrhage study. *Stroke* 2015; 46:2100-2106

17. Sano H, Satoh A, Murayama Y, et al. Modified world federation of neurosurgical societies subarachnoid hemorrhage grading system. *World Neurosurg* 2014; 83: 801-807
18. Wang A, Heros RC. Perspective on “modified WFNS subarachnoid hemorrhage grading system”. *World Neurosurg* 2015; 83:734-736
19. Jaja BN, Cusimano MD, Etminan N, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: A systematic review. *Neurocrit Care* 2013; 18:143-53
20. Janssen KJM, Donders ART, Harrell Jr. FE, et al. Missing covariate data in medical research: To impute is better than to ignore. *Eur J Epidemiol* 2010; 63:721-727
21. Altman DG, Vergouwe Y, Royston P, et al. Prognosis and prognostic research: Validating a prognostic model. *BMJ*. 2009; 338:1432–1435

SUPPLEMENTAL TABLES

Supplemental table 1 | Baseline patient characteristics distributed over three consecutive different timeframes

Timeframe	1998-2004		2004-2009		2010-2014	
	n	(%)	n	(%)	n	(%)
Total	462	(100)	635	(100)	523	(100)
Female	300	(65)	384	(61)	317	(61)
Median age in years (IQR)	53	(44-63)	55	(46-65)	57	(48-67)
Age						
<40 years	67	(15)	57	(9)	35	(7)
40-49 years	120	(26)	156	(25)	122	(23)
50-59 years	125	(26)	190	(30)	143	(27)
60-69 years	105	(23)	142	(22)	123	(24)
>70 years	45	(10)	90	(14)	100	(19)
History						
Previous SAH	9	(2)	11	(2)	11	(2)
Hypertension	71	(16)	143	(23)	122	(23)
Vitamin-K antagonist	8	(2)	9	(1)	8	(2)
Platelet inhibitor	12	(3)	19	(3)	41	(8)
Initial WFNS						
1	263	(56)	317	(49)	268	(51)
2	89	(20)	114	(18)	110	(21)
3	9	(2)	12	(2)	13	(3)
4	71	(15)	106	(17)	53	(10)
5	30	(7)	86	(14)	79	(15)
WFNS after resuscitation						
1	270	(59)	321	(50)	281	(53)
2	99	(21)	125	(20)	108	(21)
3	11	(2)	12	(2)	15	(3)
4	60	(13)	104	(16)	56	(11)
5	22	(5)	73	(12)	63	(12)
SAH type						
Aneurysmal	398	(86)	492	(78)	378	(72)
Saccular	390		484		362	
Fusiform	8		8		16	
Intracranial artery dissection	1	(<1)	18	(3)	50	(10)
Perimesencephalic/non-aneurysmal	63	(14)	125	(20)	95	(18)

Supplemental table I | Continued

Timeframe	1998-2004		2004-2009		2010-2014	
	n	(%)	n	(%)	n	(%)
Aneurysm location						
Anterior cerebral arteries	174	(37)	200	(32)	140	(27)
Middle cerebral artery	92	(20)	111	(18)	85	(16)
Posterior communicating artery	60	(13)	78	(12)	64	(12)
Internal carotid arteries	13	(3)	25	(4)	31	(6)
Posterior circulation arteries	47	(10)	91	(14)	105	(20)
Perimesencephalic/non-aneurysmal	63	(14)	125	(20)	95	(18)
Unknown	13	(3)	5	(<1)	3	(<1)
Aneurysm size						
0-4.9 mm	35	(8)	106	(17)	86	(16)
5-6.9 mm	63	(14)	143	(22)	104	(20)
7-9.9 mm	49	(11)	106	(17)	94	(18)
10-19.9 mm	31	(7)	106	(17)	68	(13)
≥20 mm	5	(1)	18	(3)	7	(1)
Fusiform/intracranial dissection	9	(2)	26	(4)	66	(13)
Perimesencephalic/non-aneurysmal	63	(13)	125	(20)	95	(18)
Unknown	207	(34)	5	(<1)	3	(<1)
Modified Fisher scale						
0	12	(3)	72	(11)	78	(15)
1	77	(17)	175	(28)	121	(23)
2	90	(19)	115	(18)	81	(15)
3	40	(9)	83	(13)	67	(13)
4	99	(21)	190	(30)	176	(34)
Unknown	144	(31)	0	(0)	0	(0)
Intracerebral hematoma	73	(16)	73	(12)	52	(10)
Subdural hematoma	6	(1)	9	(1)	5	(1)
Hydrocephalus requiring CSF-drainage*	70	(15)	137	(22)	155	(30)
Early rebleeding (<72 hours)	22	(5)	34	(5)	25	(5)
Type of treatment						
Endovascular	63	(14)	240	(37)	259	(49)
Neurosurgical	270	(57)	158	(25)	69	(13)
No treatment	66	(15)	112	(18)	100	(29)
Perimesencephalic/non-aneurysmal	63	(14)	125	(20)	95	(18)

IQR=Interquartile range; SAH=subarachnoid hemorrhage; WFNS=World Federation of Neurosurgeons Societies SAH grading scale. * External CSF drainage ≤ 24 hours after ictus and before treatment.

Supplemental table II | The distribution of functional outcome according to the modified Rankin Scale (mRS), in the three consecutive timeframes

	mRS	1998-2003 n=441 (100)	2004-2009 n=614 (100)	2010-2014 n=513(100)
Good, n (%)	0	127 (29)	155 (25)	124 (24)
	1	134 (30)	167 (28)	150 (29)
	2	54 (12)	74 (12)	67 (13)
	3	25 (6)	58 (9)	39 (8)
	Total	340 (77)	454 (74)	380 (74)
Poor, n (%)	4	24 (5)	46 (8)	40 (8)
	5	4 (1)	7 (1)	11 (2)
	6	73 (17)	107 (17)	82 (16)
	Total	101 (23)	160 (26)	133 (26)

mRS= modified Rankin scale

Chapter 5.

Prediction of outcome after aneurysmal subarachnoid hemorrhage: introduction of the SAFIRE grading scale

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ABSTRACT

Background

Early prediction of clinical outcome after aneurysmal subarachnoid hemorrhage (aSAH) is still lacking accuracy. In this observational cohort study, we aimed to develop and validate an accurate bedside prediction model for clinical outcome after aSAH, to aid decision-making at an early stage.

Methods

For development of the prediction model, a prospectively kept single-center cohort of 1215 aSAH patients, admitted between 1998 and 2014, was used. For temporal validation, a prospective cohort of 224 consecutive aSAH patients from the same center, admitted between 2015 and 2017, was used. External validation was performed using the International Subarachnoid Aneurysm Trial (ISAT) database (2143 patients). Primary outcome measure was poor functional outcome 2 months after aSAH, defined as modified Rankin Scale score 4-6. The model was constructed using multivariable regression analyses. Performance of the model was examined in terms of discrimination and calibration.

Results

The final model included four predictors independently associated with poor outcome after two months: age, WFNS-grade after resuscitation, aneurysm size and Fisher grade. Temporal validation showed high discrimination (AUC 0.90, 95% CI 0.85-0.94), external validation showed fair to good discrimination (AUC 0.73, 95% CI 0.70-0.76). The model showed good calibration in both validation cohorts. The SAFIRE-grading scale was derived from the final model: (S)ize of the aneurysm, (A)ge, (FI)sher grade, WFNS after (RE)suscitation.

Conclusion

The SAFIRE-grading scale is an accurate, generalizable and easily applicable model for early prediction of clinical outcome after aSAH.

INTRODUCTION

Early and reliable prediction of the patients' outcome after SAH is important in clinical practice for decision-making regarding treatment options, but also for providing information for the patients and their families. Despite the development of multiple grading scales, their clinical usefulness is limited, mostly because of lack of accuracy and generalizability.¹⁻³ Recently, Jaja et al. developed multiple prediction models for outcome after aneurysmal SAH.⁴ However, the use of these multiple models is confusing and the inclusion of poorly definable variables such as hypertension, make the clinical applicability questionable.

Clinical decisions are still largely based on the initial neurological condition of the patient using the WFNS SAH grading scale.⁵ However, as mentioned before, the use of the WFNS grade alone leads to overly pessimistic prognoses, especially in poor-grade patients.⁶ In chapter 4, it has been shown that the WFNS score assessed after neurological resuscitation (rWFNS) is a significant better predictor for outcome compared to the initial WFNS score. Also four other variables associated with clinical outcome were identified: age, aneurysm size, amount of blood on the initial CT scan and the presence of intracerebral hematoma.

Although several other variables have been identified as predictor for clinical outcome, these have not all been confirmed in other studies and are not all available at an early stage.^{3,7-12} In this chapter, we aimed to develop and validate a bedside prediction model for clinical outcome after aSAH, using a prospectively kept cohort for temporal validation as well as data from the International Subarachnoid Aneurysm Trial (ISAT) database for external validation.¹³

METHODS

Derivation cohort

For development of the prediction model, data from our prospectively maintained observational cohort was used, including 1620 SAH patients admitted to our university neurovascular center between January 1998 and December 2014. The treatment protocol and method of data collection can be found in chapter 4.

According to our treatment protocol, withdrawal of care (including life-support) in patients with an infaust prognosis within 72 hours after the ictus was only permitted after neurosurgical resuscitation. An infaust prognosis refers to a state where a patient will inevitably die, for example, when diagnosed as brain dead.

For the development of this model we only included aneurysmal SAH (aSAH) patients, excluding 384 patients with non-aneurysmal SAH or intracranial dissection. Also, we excluded 21 patients who died before CTA or DSA could be performed to identify an aneurysm. As a result, 1215 patients were considered eligible for inclusion.

Temporal validation cohort

Temporal validation was performed using the prospectively kept cohort of 224 aSAH patients admitted to the University Medical Center Groningen between January 2015 and December 2017. Treatment protocol and methods of data collection are similar to that of the derivation cohort (chapter 4).

External validation cohort

For external validation, the International Subarachnoid Aneurysm Trial (ISAT) dataset was used. ISAT was a randomized controlled trial comparing the safety and efficacy of endovascular coiling versus neurosurgical clipping. The dataset includes 2143 patients with aSAH, recruited between 1994 and 2002 in 43 international centers. ISAT included only patients considered eligible for both treatment modalities; patients who died before randomization were not included. In the ISAT cohort, the WFNS grade was prospectively collected at time of randomization. As in ISAT the median time between ictus and randomization was 2 days, it is likely that live-saving neurological resuscitation is performed before randomization.¹³ Therefore, the WFNS at time of randomization in ISAT is considered the equivalent of the rWFNS.

Outcome measures

The primary outcome measure was poor functional outcome two months after SAH according to the modified Rankin Score (mRS). Poor outcome was defined as a mRS of 4, 5, or death (mRS 6). In all cohorts, the mRS score was assessed by a validated questionnaire during standardized outpatient follow-up visits.

Model development

The following variables were prospectively collected in the derivation cohort: date of ictus, age at time of SAH, sex, history of SAH, hypertension, rWFNS grade, symptomatic aneurysm size and location, amount of blood on initial CT scan, acute hydrocephalus requiring initiation of CSF drainage within 24 hours after ictus, type and time of aneurysm repair, and early rebleeding. Age of the patient and the size of the symptomatic aneurysm were classified according to the PHASES study.¹⁴ For validation purposes, the Fisher scale was used instead of the modified Fisher scale to classify the amount of blood on the CT-scan (table 1).¹⁵ As a sensitivity analysis, we analyzed the model performance in the derivation cohort, using the mFisher scale.

Univariate logistic regression analysis was performed after which all variables with a $p < 0.157$ were included in the multivariable logistic regression analysis.¹⁶ Backwards stepwise selection was applied to obtain the best predictive model, a cut-off point of $p < 0.10$ was used for inclusion in the final model.¹⁶ Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Bootstrapping with 100 replacement samples was performed to validate the model internally. Since data are collected over a relatively long period of time, and clinical outcome of SAH patients has improved significantly in recent years,¹⁷ additional sensitivity analyses were performed in three consecutive time-frames (1998-2003, 2004-2009 and 2010-2014).

Model performance

Model performance was assessed in terms of discrimination and calibration. Discrimination of the model is the ability to distinguish between patients with a poor versus good outcome and was examined using Area Under the receiver operating characteristic Curve (AUC) with corresponding 95% CI. Calibration of the model is the ability to predict the actual outcome in patients and was examined using likelihood-ratio tests and visualized with calibration belt graphs.¹⁸ Model performance was compared to the nowadays used WFNS grading scale and the recently developed SAHIT prediction models.⁴

Table 1 | Fisher scale for classification of amount of subarachnoid blood on the CT-scan.

Grade	Description
Grade 1	No subarachnoid or intraventricular hemorrhage present
Grade 2	Diffuse thin (<1 mm) subarachnoid hemorrhage, no blood clots
Grade 3	Localized blood clots and/or layers of subarachnoid blood (>1 mm)
Grade 4	Intracerebral or intraventricular hemorrhage present, with or without diffuse subarachnoid hemorrhage

Risk-chart

The contribution of each covariate for poor outcome was calculated by conversion of the final regression Beta coefficients to a nominal value, after which for each score the sum-scores of the predictive covariates were calculated in the derivation cohort. These sum-scores were then compared with the predicted probability for poor outcome of each case, after which a risk-chart for poor outcome was constructed.¹⁹

Missing data

In the derivation cohort, data was missing for aneurysm size (16%), Fisher grade (7%), and outcome (3%). Multiple imputation (10 datasets) with multivariable regression analysis was used to impute these missing variables. Complete case analysis was performed as

sensitivity analysis. In the temporal validation cohort, aneurysm size and location were unknown for two patients (1%) due to death before CTA or DSA. Furthermore, the mRS score for 5 patients was missing due to loss of follow-up. In the ISAT cohort, the mRS score at 2 months after aSAH was missing for 15 patients. For 8 of these patients, mRS scores at a later time are known, which were used to impute for the missing mRs after two months. In the end, outcome was considered unknown for 7 patients (1%). Since the percentage of missing data in both validation cohorts is statistically negligible,¹⁶ complete case analyses were used in the validation process. A two-tailed P-value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc.) and STATA version 15.0 (Statacorp, College Station, TX).

RESULTS

The distribution of the patients' characteristics and prognostic factors for the derivation cohort are shown in table 2. The majority of the patients were female (67%) and median age was 55 years (IQR 46-65). Most aneurysms were located in the anterior circulation (42%). Poor outcome after two months was observed in 28% of the patients (table 3). In 90 patients (7%), the prognosis was determined infaust within the first 24h, after which life-support was withdrawn, leading to death.

Results of the logistic regression are presented in Table 4. Age, rWFNS grade, aneurysm size and Fisher grade were independent predictors for poor outcome. Internal validation and complete case analysis showed no bias (data not shown). The final model had an AUC of 0.83 (95% CI 0.80-0.85, figure 1a) and calibration showed agreement between predicted and observed outcome (figure 2a). Sensitivity analysis showed similar results in the three consecutive timeframes with increasing discriminative performance over the years (time frame 1998-2003: AUC 0.82, 95% CI 0.77-0.87; time frame 2004-2009: AUC 0.82, 95% CI 0.77-0.86; time frame 2010-2014: AUC 0.88, 95%CI 0.84-0.92). When using the mFisher scale instead of the Fisher scale, the model performance is comparable (AUC 0.84, 95% CI 0.80-0.87).

The baseline patient characteristics for both validation cohorts are shown in table 2. Median age was 58 years (IQR 50-67) in the temporal validation cohort and 52 years (IQR 44-60) in the ISAT validation cohort. The ISAT cohort included patients with smaller aneurysms, which were more often located in the anterior region. Furthermore, ISAT clearly had a smaller proportion of patients with a rWFNS of 4-5. Poor outcome after two months was observed in 36% of the patients in the temporal validation cohort and in 17% of the ISAT cohort (table 3).

Receiver Operating Characteristic (ROC) curves for both validation cohorts are shown in figure 1b and 1c. The model showed an AUC of 0.90 (95% CI 0.85-0.94) in temporal validation, and 0.73 (95% CI 0.70-0.76) in external validation. Figure 2b and 2c show the calibration belt graphs indicating the model fit. In temporal validation, there was agreement between expected and observed poor outcome. A similar result was seen in external validation, with a slight underestimation of the observed poor outcome in the low-risk patients. For the high-risk patients, there was agreement between expected and observed poor outcome.

As comparison, discriminative performance of the currently used WFNS scale is considerably lower in our derivation cohort (AUC 0.77, 95% CI 0.74-0.80). Discriminative performance of the neuroimaging model of SAHIT in our derivation cohort was comparable to our developed model (AUC 0.83, 95% CI 0.80-0.85).

Table 5 shows the SAFIRE risk chart: ((S)ize of the aneurysm, (A)ge, (FI)sher grade, WFNS after (RE)suscitation), based on the Beta coefficients derived from the regression analyses. After calculation of the sum score, the corresponding SAFIRE grade can be derived from the grading scale (table 6). The regression equation with the Beta coefficients and corresponding intercept (constant) is provided in textbox 1.

Table 2 | Baseline patient characteristics

	Groningen Derivation Cohort n=1215	Groningen Validation Cohort n=224	ISAT Validation Cohort n=2143
Timeframe (years)	377(31)	0	2143 (100)
1998-2003	478 (39)	0	0
2004-2009	360 (30)	0	0
2010-2014	0	224 (100)	0
2015-2017	814 (67)	157 (70)	1345 (63)
Female sex			
Median age in years (IQR)	55 (45-64)	58 (51-68)	52 (44-60)
Age			
<40 years	125 (10)	17 (8)	341 (16)
40-49 years	295 (24)	31 (14)	539 (25)
50-59 years	350 (29)	76 (34)	719 (34)
60-69 years	269 (22)	50 (22)	408 (19)
>70 years	176 (15)	50 (22)	136 (6)
History			
Previous SAH	26 (2)	10 (4)	137 (6)
Hypertension	274 (23)	77 (34)	NA
WFNS grade after resuscitation			
1	572 (47)	84 (37)	1335 (62)
2	286 (23)	47 (21)	549 (26)
3	33 (3)	15 (7)	134 (6)
4	193 (16)	26 (12)	74 (4)
5	131 (11)	52 (23)	51 (2)
Aneurysm location			
Anterior cerebral arteries	505 (42)	84 (38)	1085 (50)
Middle cerebral arteries	279 (23)	52 (23)	303 (14)
Posterior communicating arteries	199 (16)	39 (17)	535 (25)
Internal carotid arteries	47 (4)	8 (4)	162 (8)
Posterior circulation arteries	185 (15)	41 (18)	58 (3)
Aneurysm size			
0-4.9 mm	227 (19)	58 (26)	734 (34)
5-6.9 mm	310 (26)	45 (20)	685 (32)
7-9.9 mm	249 (20)	50 (23)	432 (20)
10-19.9 mm	205 (17)	61 (26)	279 (13)
≥20 mm	30 (2)	8 (4)	13 (1)
Unknown	194 (16)	2 (1)	0

Table 2 | Continued

	Groningen Derivation Cohort n=1215	Groningen Validation Cohort n=224	ISAT Validation Cohort n=2143
Fisher grade			
1	37 (3)	9 (4)	114 (5)
2	259 (21)	36 (16)	360 (17)
3	120 (10)	19 (9)	902 (42)
4	711 (60)	160 (71)	753 (35)
Unknown	88 (7)	0	14 (1)
Intracerebral hematoma	184 (15)	61 (27)	88 (4)
Subdural hematoma	17 (2)	15 (7)	NA
Hydrocephalus requiring CSF drainage*	288 (24)	101 (31)	257 (12)
Early rebleeding (<72 hours)	77 (7)	35 (11)	50 (2) †
Type of treatment			
Endovascular	534 (44)	141 (63)	1073 (50) ‡
Neurosurgical	494 (41)	39 (17)	1071 (50) ‡
No treatment	187 (15)	44 (20)	0

IQR=Interquartile range; SAH=subarachnoid hemorrhage; WFNS=World Federation of Neurosurgical Societies grading scale. NA= Not applicable

* Drainage ≤ 24h after ictus and before treatment † Rebleeding before treatment ‡ Treatment as randomized

Table 3 | Distribution of functional outcome after two months according to the modified Rankin Scale.

Functional outcome	modified Rankin Scale	Groningen Derivation Cohort n= 1215	Groningen Validation Cohort n=224	ISAT Validation Cohort n=2143
Good, n (%)	0	252 (20)	18 (8)	348 (16)
	1	309 (25)	70 (31)	586 (27)
	2	177 (15)	28 (13)	529 (25)
	3	109 (9)	22 (10)	296 (14)
	Total	847(69)	138 (62)	1759 (82)
Poor, n (%)	4	98 (8)	29 (13)	82 (4)
	5	20 (2)	2 (1)	133 (6)
	6	216 (18)	50 (22)	162 (7)
	Total	334 (28)	81 (36)	377 (17)
	Missing, n (%)	34 (3)	5 (2)	7 (1)

Table 4 | Results of the univariate and multivariable logistic regression for poor outcome two months after aneurysmal SAH in the Groningen derivation cohort.

n=1215	Univariate analysis			Multivariable analysis †		
	OR	95% CI	p-value*	aOR	95% CI	p-value*
Age			<0.001			<0.001
<40 years	1.0			1.0		
40-49 years	1.4	0.8-2.4	0.21	1.2	0.6-2.3	0.63
50-59 years	1.6	0.9-2.7	0.08	1.4	0.8-2.7	0.27
60-69 years	2.3	1.3-3.9	0.003	2.0	1.0-3.7	0.04
>70 years	4.6	2.6-8.0	<0.001	5.0	2.6-9.7	<0.001
Male sex	1.1	0.9-1.5	0.36			
History						
Previous SAH	1.3	0.6-3.0	0.47			
Hypertension	1.2	0.9-1.7	0.17			
WFNS grade after resuscitation			<0.001			<0.001
1	1.0			1.0		
2	2.7	1.8-3.9	<0.001	2.2	1.5-3.3	<0.001
3	4.2	1.9-9.1	<0.001	3.0	1.3-7.1	0.01
4	8.2	5.5-12.2	<0.001	6.7	4.3-10.5	<0.001
5	19.5	12.2-31.2	<0.001	15.1	9.0-25.2	<0.001
Aneurysm location			0.49			
Anterior cerebral arteries	1.0					
Middle cerebral arteries	1.1	0.8-1.5	0.74			
Posterior communicating arteries	1.3	0.9-1.8	0.19			
Internal carotid arteries	0.9	0.4-1.8	0.69			
Posterior circulation arteries	1.2	0.8-1.8	0.30			

Table 4 | Continued

n=1215	Univariate analysis			Multivariable analysis †		
	OR	95% CI	p-value*	aOR	95% CI	p-value*
Aneurysm size			<0.001			<0.001
0-4.9 mm	1.0			1.0		
5-6.9 mm	0.8	0.6-1.3	0.38	0.9	0.5-1.5	0.65
7-9.9 mm	1.0	0.6-1.6	0.94	0.9	0.6-1.6	0.84
10-19.9 mm	1.7	1.1-2.6	0.009	1.6	1.0-2.7	0.05
≥20 mm	6.5	2.3-18.1	<0.001	8.0	2.3-27.5	0.002
Fisher grade			<0.001			0.001
1	1.0			1.0		
2	0.6	0.2-1.7	0.35	0.5	0.2-1.8	0.31
3	1.7	0.6-4.9	0.35	1.0	0.3-3.8	0.96
4	3.6	1.4-9.3	0.09	1.6	0.5-5.1	0.41
Subdural hematoma	2.3	0.87-6.0	0.09			
Hydrocephalus requiring CSF-drainage ‡	3.1	2.3-4.1	<0.001			

OR=Odds ratio; CI=Confidence Interval; aOR=adjusted Odds Ratios; SAH=Subarachnoid hemorrhage; WFNS=World Federation of Neurosurgical Societies; CSF=Cerebrospinal Fluid Drainage * Derived from Likelihood tests † Effect estimates from the multivariable regression are adjusted for all other variables in the model ‡ Drainage ≤ 24h after ictus and before treatment

Table 5 | Predictors composing the SAFIRE risk chart.

Predictor	Points
(S)ize of the aneurysm	
<10 mm	0
10-19.9 mm	2
≥20 mm	6
(A)ge	
≤50 years	0
50-60 years	1
60-70 years	2
≥70 years	5
(F)isher grade	
1-3	0
4	2
(RE)uscitated WFNS grade	
1	0
2	2
3	3
4	6
5	9

WFNS=World Federation of Neurosurgical Societies

Table 6 | The SAFIRE grading scale

SAFIRE grade	Points	Risk of poor outcome	%
I	0-2	Low risk	<10
II	3-5	Low-intermediate risk	10-25
III	6-8	Intermediate risk	25-50
IV	9-15	Intermediate-high risk	50-90
V	>15	High risk	>90

Figure 1a.

Figure 1b.

Figure 1c.

Figure 1a-c | Receiver Operating Characteristic (ROC) graph representing the discriminative value of the prediction model in the pooled Groningen derivation cohort (a), Groningen validation cohort (b) and ISAT validation cohort (c).

Figure 2a.

Figure 2b.

Figure 2c.

Figure 2a-c | Calibration belt graph representing the goodness of fit of the prediction model in the pooled Groningen derivation cohort (a), Groningen validation cohort (b) and ISAT validation cohort (c).

Textbox 1 | Calculation of the probability for poor outcome 2 months after aneurysmal subarachnoid hemorrhage.

The probability of a poor outcome 2 months after aneurysmal subarachnoid hemorrhage (%) is calculated as:

$$\text{Probability (\%)} = 100\% * \frac{\exp(EQ)}{1+\exp(EQ)}$$

EQ represents the following equation derived from our final logistic regression model, including the beta coefficients from the independent predictors and the constant, which is the average of the patients' risk factors.

$$EQ = -2.86 \text{ (constant)} + 0.36 \text{ (if age 50-59)} + 0.68 \text{ (if age 60-69)} + 1.60 \text{ (if age } \geq 70) + 0.78 \text{ (if rWFNS 2)} + 1.09 \text{ (if rWFNS 3)} + 1.91 \text{ (if rWFNS 4)} + 2.7 \text{ (if rWFNS 5)} + 0.49 \text{ (if size 10-20mm)} + 2.08 \text{ (if size } \geq 20\text{mm)} + 0.49 \text{ (if Fisher 4)}$$

Example:

Consider a 60-year old woman admitted with aneurysmal subarachnoid hemorrhage and WFNS grade of 2 after resuscitation (rWFNS). The radiological imaging reveals an aneurysm with a size of 11mm and the amount of blood graded as Fisher 4. EQ will be calculated as:

$$EQ = -2.86 \text{ (constant)} + 0.68 \text{ (if age 60-69)} + 0.78 \text{ (if rWFNS 2)} + 0.49 \text{ (if size 10-20mm)} + 0.49 \text{ (if Fisher 4)} = -0.42$$

The predicted probability is consequently calculated as:

$$\text{Probability (\%)} = 100\% * \frac{\exp(-0.42)}{1+\exp(-0.42)} = 40\%$$

This woman has a 40% chance of poor outcome 2 months after her initial ictus.

DISCUSSION

We aimed to develop a model for prediction of outcome after aSAH. We identified four easily obtainable variables at presentation to be independently associated with poor outcome after two months: age, rWFNS grade, aneurysm size and Fisher grade. The model showed good discriminative performance and model fit, also in both validation cohorts. Together, these four variables were used to develop the SAFIRE grading scale (Size of the aneurysm, Age, Fisher grade, and WFNS grade after Resuscitation).

To be considered clinically useful, prediction models need to include clinically relevant parameters which are easy and early to obtain. More importantly, the model needs accuracy and generalizability, which can only be obtained after external validation.²⁰ In contrast to published prognostic models, where external validation is lacking,¹ this model has been externally validated, showing good accuracy and generalizability. When compared to the still widely used WFNS scale, the current model discriminates considerably better.

The observational nature of the derivation cohort contributes to the generalizability of our model, since all patients with aneurysmal SAH are included, and thus no selection bias exists, while most other prediction models are developed on trial data.^{11,21,22} Trials in general include select patient populations, and may therefore not always be suitable for development of prediction models. In contrast, for external validation, clinical trial data is very useful, although performance is often poorer compared to cohort data.^{4,21,22} This selection bias often observed in clinical trials may explain the lower discriminative performance of the SAFIRE grading scale in the ISAT cohort.

Another explanation for the relatively lower performance of the model in the ISAT cohort may be the use of relatively outdated data. The last ISAT patients were recruited in 2002, and over the past decades treatment and outcome of patients with aSAH has significantly improved.^{13,23} Besides improvement in diagnostic modalities and treatment techniques, a shift in treatment modality used to treat aneurysms has occurred. In the past, the large majority of aneurysms were treated with neurosurgical clipping, whereas nowadays approximately 80% are secured via endovascular coiling. The same phenomenon is also observed within the derivation cohort. Although our model is developed on the basis of a cohort collected over a significant time span, the discrimination in the more recent timeframe is better when compared to the older timeframes. The excellent performance in the most recent cohort from Groningen (2015-2017) further attributes to the validity of the SAFIRE grading scale in current aSAH patients.

Comparison with other prediction models

Risselada et al. developed in 2010 a prognostic model for mortality alone after aSAH, based on the ISAT cohort.²² This model yielded an AUC of 0.73. However, when tested externally in another selected group of aSAH patients by Dijkland et al., the model did not fit well.² Moreover, the use of mortality as the sole endpoint for the prediction model, which is also used in the SAHIT study⁴, is clinically less useful when compared to poor clinical outcome.

Recently Blessings et al. developed multiple prediction models for outcome after aSAH, based on the SAHIT dataset.⁴ The SAHIT prediction model is comparable to SAFIRE in performance, but the latter is easier to use as a bedside grading model. We created one prediction model, instead of six, with only four well defined variables. Furthermore, the inclusion of the predictor hypertension in the SAHIT models is debatable, as it is poorly defined.

Some variables associated with poor outcome, such as laboratory parameters or variables, obtained in a later stage in the aSAH course, such as treatment or DCI, were not included in our model.^{4,7-10} Although the inclusion of these variables may slightly improve the prognostic value, it is important to consider we aimed to develop a prediction model to aid decision-making at an early stage before actual treatment.

Strengths and limitations

Some limitations of the study need to be addressed. Firstly, two of the predictors in our model, aneurysm size and Fisher grade, are sensitive for measurement errors. Since ISAT contains multicenter data of these variables, similar measurement errors exist in this cohort. Hence, the good external validation suggests that this does not affect the reliability of the model. Secondly, complications in the course after aSAH, such as rebleeding of the aneurysm or delayed cerebral ischemia (DCI) are not included in the model but can influence the outcome significantly.⁵ Thirdly, for validation purposes, the Fisher scale was used instead of the mFisher scale. Nowadays, the mFisher scale is preferred because the grades are better defined, and it is more accurate in the prediction of delayed cerebral ischemia. However, the mFisher has not been proven to be more accurate in prediction of outcome as such.¹⁵ In addition, in our model, the performance of both scales is comparable.

Fourthly, the rWFNS score was not collected in ISAT. Because the WFNS score in ISAT was determined after averagely 2 days, we considered this WFNS score as equivalent of the rWFNS score. It is however important to note that this is only an approximation, performed for validation purposes. Last, it is important to consider that patients who died because of withdrawal of life-support in case of an infaust prognosis, are also included

in this model. The decision to stop life-support because of an infaust prognosis can be considered a self-fulfilling prophecy to some extent and as such may contribute to confounding in prediction models.²⁴ Ideally, a prediction model is developed in a population in which no patients are withdrawn of care, which is unfortunately rare in clinical practice.

There are several strengths of this study. Firstly, the cohort used for model development is one of the largest unselected observational cohorts of aSAH patients available. Secondly, the identified predictors are all easy obtainable at an early stage, which makes this model useful as a bed-side predictive scale. Most importantly, the model shows accuracy in both temporal and external validation, outperforms currently used models including the WFNS, and can therefore be considered widely applicable.

Clinical implications

For physicians, reliable prediction of clinical outcome in aSAH patients soon after admission is of utmost importance for decision-making about treatment. In clinical practice, aneurysm repair is sometimes delayed or withheld because treatment is seen as futile, whereas the patient actually has a reasonable chance of a good outcome. This is, recently shown by Goldberg et al, especially the case in elderly patients with low WFNS grades (IV and V). In this study, they showed that these patients can have favorable outcomes when maximal treatment is given.²⁵ The SAFIRE grading scale is more accurate compared with the nowadays used WFNS grading scale, of which it is known that 20% of the WFNS grade V patients recover without any neurological deficits.⁷ Withholding aneurysm repair is keeping these patients unnecessary at risk for aneurysm rebleeding.²⁶ Because the SAFIRE grading scale especially identifies poor-grade patients more accurately, it can help physicians with difficult decisions about treatment for these patients. The importance of accurate identification of true poor-grade patients is also illustrated by some current questions about type and timing of aneurysm repair in these patients. It is known that in good-grade patients, coiling is favorable over clipping, but for poor-grade patients firm evidence is lacking.²⁷ Also, it is unclear whether poor-grade patients benefit from early treatment (<24 hours after ictus), which is nowadays more often standard for good-grade patients.²⁸ The SAFIRE grading scale can aid with better identification of poor-grade patients and can thus be used in future trials about these subjects. Hopefully, this will lead to better treatment of these patients in clinical practice. Besides WFNS grading scale, other developed prediction models are rarely used not only because of lack of accuracy but also lack of ease to use. The SAFIRE grading scale excels in simplicity and can be used by all physicians involved in the treatment of aSAH patients. In future research, we encourage further validation of the grading scale, to establish an optimal prediction model with broad support throughout the neurovascular community.

Conclusions

The SAFIRE-grading scale is an accurate, generalizable and easily applicable model for early prediction of clinical outcome after aSAH. The bedside grading scale identifies poor-grade patients better compared to the nowadays used WFNS score, and can therefore aid decision-making regarding treatment at an early stage.

REFERENCES

1. Jaja BNR, Cusimano MD, Etminan N, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: A systematic review. *Neurocrit. Care.* 2013; 18:143–153.
2. Dijkland SA, Roozenbeek B, Brouwer PA, et al. Prediction of 60-day case fatality after aneurysmal subarachnoid hemorrhage: External validation of a prediction model. *Crit. Care Med.* 2016; 44:1523–1529.
3. Abulhasan YB, Alabdulraheem N, Simoneau G, et al. Mortality after Spontaneous Subarachnoid Hemorrhage: Causality and Validation of a Prediction Model. *World Neurosurg.* 2018; 112:e799–e811.
4. Jaja BNR, Saposnik G, Lingsma HF, et al. Development and validation of outcome prediction models for aneurysmal subarachnoid hemorrhage: the SAHIT multinational cohort study. *BMJ.* 2018; 362:k4079.
5. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2012; 43:1711–1737.
6. Haug T, Sorteberg A, Finset A, et al. Cognitive functioning and health-related quality of life 1 year after aneurysmal subarachnoid hemorrhage in preoperative comatose patients. *Neurosurgery.* 2010; 66:475–484.
7. Salary M, Quigley MR, Wilberger JE. Relation among aneurysm size, amount of subarachnoid blood, and clinical outcome. *J. Neurosurg.* 2007; 107:13–17.
8. Turck N, Vutskits L, Sanchez-Pena P, et al. A multiparameter panel method for outcome prediction following aneurysmal subarachnoid hemorrhage. *Intensive Care Med.* 2010; 36:107–115.
9. Mocco J, Ransom ER, Komotar RJ, et al. Preoperative Prediction of Long-term Outcome in Poor-grade Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery.* 2006; 59:529–538.
10. Claassen J, Vu A, Kreiter KT, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. *Crit. Care Med.* 2004; 32:832–838.
11. Germanson TP, Lanzino C, Kongable GL, Torner JC, Kassell TNF. Risk classification after aneurysmal subarachnoid hemorrhage. *Surg Neurol.* 1998; 49:155–63.
12. Le Roux PD, Elliott JP, Newell DW, et al. Predicting outcome in poor-grade patients with subarachnoid hemorrhage: a retrospective review of 159 aggressively managed cases. *J. Neurosurg.* 1996; 85:39–49.
13. Molyneux AJ, Kerr RS, Yu LM, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomized trial. *Lancet.* 2002; 360:1267–74.
14. Greving JP, Wermer MJH, Brown RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: A pooled analysis of six prospective cohort studies. *Lancet Neurol.* 2014; 13:59–66.
15. Fisher CM, Kistler J.P, Davis J.M. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery.* 1980; 61-9

16. Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. *BMJ*. 2009; 338:1373–1377.
17. Nieuwkamp DJ, Vaartjes I, Algra A, et al. Age- and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the Netherlands. *Int. J. Stroke*. 2013; 8:90–94.
18. Nattino G, Lemeshow S, Phillips G, et al. Assessing the calibration of dichotomous outcome models with the calibration belt. *Stata J*. 2017; 17:1003–1014.
19. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariable data for clinical use: The Framingham Study risk score functions. *Stat. Med*. 2004; 23:1631–1660.
20. Altman DG, Vergouwe Y, Royston P, et al. Prognosis and prognostic research: Validating a prognostic model. *BMJ*. 2009; 338:1432–1435.
21. Rosen DS, Macdonald RL, Batjer HH, et al. Grading of Subarachnoid Hemorrhage: Modification of the World Federation of Neurosurgical Societies Scale on the Basis of Data for a Large Series of Patients. *Neurosurgery*. 2004; 54:566–576.
22. Risselada R, Lingsma HF, Bauer-Mehren A, et al. Prediction of 60 day case-fatality after aneurysmal subarachnoid hemorrhage: Results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur. J. Epidemiol*. 2010; 25:261–266.
23. Mukhtar TK, Molyneux AJ, Hall N, et al. The falling rates of hospital admission, case fatality, and population-based mortality for subarachnoid hemorrhage in England, 1999–2010. *J. Neurosurg*. 2016; 125:698–704.
24. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of Support in Intracerebral Hemorrhage May Lead to Self-Fulfilling Prophecies. *Neurology*. 2001; 56:766–72.
25. Goldberg J, Schoeni D, Mordasini P, et al. Survival and outcome after poor-grade aneurysmal subarachnoid hemorrhage in elderly patients. *Stroke*. 2018; 49:2883–2889.
26. van Donkelaar CE, Bakker NA, Veeger NJ, et al. Predictive factors for rebleeding after aneurysmal subarachnoid hemorrhage: rebleeding aneurysmal subarachnoid hemorrhage study. *Stroke*. 2015; 46:2100–2106.
27. Lindgren A, Vergouwen MD, van der Schaaf I, et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid hemorrhage. *Cochrane Database Syst Rev*. 2018; 8:CD003085.
28. Rawal S, Alcaide-Leon P, Macdonald RL, et al. Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid hemorrhage: inconsistent results of early treatment within 1 day. *J Neurol Neurosurg Psychiatry*. 2017; 88:241–248.

Chapter 6.

The impact of treatment delay on outcome in the international Subarachnoid Aneurysm Trial

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ABSTRACT

Background

ISAT demonstrated that 1 year after aneurysmal subarachnoid hemorrhage (aSAH), coiling resulted in a significantly better clinical outcome than clipping. After 5 years, this difference did not reach statistical significance, but mortality was still higher in the clipping group. Here, we present additional analyses, reporting outcome after excluding pre-treatment deaths.

Methods

Outcome measures were death with or without dependency at 1 and 5 years after treatment, after exclusion of all pre-treatment deaths. Treatment differences were assessed using relative risks. With sensitivity and exploratory analyses, the relation between treatment delay and outcome was analyzed.

Results

After exclusion of pre-treatment deaths, at 1-year follow-up coiling was favorable over clipping for death or dependency (RR 0.77; 95%CI 0.67-0.89), but not for death alone (RR 0.88; 95%CI 0.66-1.19). After 5 years, no significant differences were observed, neither for death or dependency (RR 0.88; 95%CI 0.77-1.02), nor for death alone (RR 0.82; 95%CI 0.64-1.05). Sensitivity analyses showed a similar picture. In good-grade patients, coiling remained favorable over clipping in the long-term. Time between randomization and treatment was significantly longer in the clipping arm (mean 1.7 versus 1.1 days; $p < 0.0001$), during which 17 patients died because of rebleeding vs. 6 pretreatment deaths in the endovascular arm (RR=2.81; 95%CI 1.11-7.11).

Conclusions

These additional analyses support the conclusion of ISAT that at 1-year follow-up after aSAH coiling has a better outcome than clipping. After 5 years, with pre-treatment mortality excluded, the difference between coiling and clipping is not significant. The high number of pre-treatment deaths in the clipping group highlights the importance of urgent aneurysm treatment to prevent early rebleeding.

INTRODUCTION

The treatment of aneurysmal subarachnoid hemorrhage (aSAH) has significantly changed following publication of the results of the International Subarachnoid Aneurysm Trial (ISAT). ISAT demonstrated that in patients considered eligible for both treatments, clinical outcome at 1 year after aSAH was significantly better with endovascular coiling than with neurosurgical clipping.^{1,2} Also after longer follow-up, the benefit in terms of death alone was significantly better with coiling.^{3,4} As a result, most neurovascular centers in Europe now preferentially use coiling.⁵

Pre-treatment rebleeding is the most serious risk to patients after aSAH, and typically occurs in the early days after the ictus.⁶ Therefore, guidelines recommend to treat all aSAH patients as soon as feasible, preferably not later than 72h after the ictus.^{7,8} In the 1990's some centers preferred to delay neurosurgical clipping for some patients to avoid the vasospasm period, and allow for better operative conditions. As a result, in ISAT, there was a significant difference in the interval between randomization and treatment between the two arms (mean 1.7 days for neurosurgical clipping versus 1.1 days for endovascular coiling).¹ More patients with neurosurgical allocation suffered pre-treatment rebleeding compared with coiling allocation.⁹⁻¹³

The standard analysis in a prospective randomized controlled trial is intention-to-treat (ITT) analysis. The ITT-method is appropriate for a randomized trial when all events after randomization are considered an intrinsic part of the allocated treatment. However, delaying neurosurgical clipping is nowadays no longer considered appropriate. As such, a significant interest, particularly in the neurosurgical community, has been noted for an additional analysis considering time-to-treatment.^{10,12}

Current CONSORT-guidelines recommend that in addition to ITT analysis, additional analyses that not have been pre-specified should be accurately described to allow readers to interpret the effect of an intervention.¹⁴ In this study, we present such additional analyses, investigating the impact of death and rebleeding after randomization but before treatment on outcomes in ISAT.

METHODS

Patients

ISAT included 2143 patients with aSAH considered equally eligible for both coiling and clipping. Inclusion criteria and treatment protocol are detailed in the primary paper.¹

ISAT included 1644 patients (77%) from 22 UK centers and 499 patients (23%) from 22 non-UK centers. All patients had a follow-up annually for 5 years.

Outcome measures

The primary outcome was death or dependency, measured at 1 and 5 years following aSAH. The secondary outcome was death alone, also measured at 1 and 5 years following aSAH. The modified Rankin Scale (mRS) was used to classify the clinical outcome, with dependency defined as mRS score of 3-5.¹⁵

Rebleeding was in the original protocol defined as the occurrence of symptoms of clinical deterioration with confirmation by the increase of blood on a subsequent CT-scan. The protocol further stated that allocation was to a policy of coiling and clipping, respectively. This recognized the presence of significant variations in the policy of the timing of neurosurgical treatment after SAH at that time.

Study design

In this study, additional analyses were made on ISAT data. We analyzed the outcome of coiling and clipping after exclusion of post-randomization pre-treatment deaths. Thus, we aimed to adjust for events that occurred before treatment initiation. Our hypothesis is that after exclusion of pre-treatment deaths, there will be no significant difference between coiling and clipping in long term.^{10,12}

We performed three additional sensitivity analyses. First, we excluded all pretreatment rebleedings, whether fatal or not. Second, we performed an as-treated analysis, in which patients were analyzed as actual treatment received, omitting untreated patients. Last, as treatment delay is more common in poor-grade patients, we performed an as-treated analysis in all patients with a good clinical condition at randomization (WFNS grade I-II).

Statistical analysis

All patients' vital status was known. For patients known to be alive, mRS scores were missing for 25 patients at 1 year (1%) and 364 patients at 5 years (17%), with no significant differences between the two groups. Most of these patients were not lost-to-follow-up and therefore missing values were imputed using mRS scores assessed at other time points. Categorical data were examined using Pearson's χ^2 tests. Mann-Whitney U tests were used to compare non-parametric data. Relative risks (RRs) were used to describe the treatment effect. A two-tailed P-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using STATA version 15.0 (Statacorp, College Station, TX).

RESULTS

Exclusion of pre-treatment deaths

1073 patients were allocated to endovascular coiling and 1070 to neurosurgical clipping (figure 1). After randomization, 27 patients died before treatment was initiated; 19 in the neurosurgical arm and 8 in the endovascular arm. The remaining patients were treated. Baseline patient characteristics of the two groups after exclusion of these patients show no significant differences (table 1). Outcome of the population after exclusion of pre-treatment deaths can be found in the supplemental material at the end of this chapter (supplemental table I). After excluding pre-treatment deaths, the RR for death or dependency after 1 year was significantly in favor of coiling ($0.77 - 95\% \text{ CI } 0.67-0.89$, table 2); the RR for death was 0.88 ($95\% \text{ CI } 0.66-1.19$). At 5 years, the difference between treatment modalities did not reach statistical significance, for either death or dependency (RR $0.88 - (95\% \text{ CI } 0.77-1.02)$, or for death alone (RR $0.82 - 95\% \text{ CI } 0.64-1.05$).

Figure 2 displays the Kaplan-Meier graph after exclusion of pre-treatment deaths. Follow-up was between 5 and 14 years. No significant difference in mortality over time between the two treatment arms was observed (log-rank test $p=0.23$).

Sensitivity analyses

Baseline patient characteristics and outcome of the populations used in the sensitivity analyses can be found in the supplements (supplemental table I-V). Fifty patients suffered a rebleeding before treatment was initiated; 31 in the neurosurgical arm and 19 in the endovascular arm. At 1 year, rebleeding resulted in 5 additional deaths; 15 patients were functionally dependent.

Figure 1 shows the population of the as-treated analysis, excluding pre-treatment deaths and analyzing cross-overs with actual treatment received. The majority of included patients ($1861/2143 - 87\%$) were in a good clinical condition at randomization. Of these, 964 (52%) actually had coiling and 897 (48%) had clipping.

Using these populations as sensitivity analyses, similar results are found (table 1). However, in good-grade patients, the long-term benefit of coiling remained (RR death or dependency $0.82 - 95\% \text{ CI } 0.71-0.96$; death alone $0.72 - 95\% \text{ CI } 0.54-0.97$).

Treatment delay

Median interval between randomization and fatal rebleeding ($n=23$) was 2 days (IQR 1-4 days), with for coiling a mean of 0.8 days (range 0-2) and for clipping a mean of 3.7 days

(range 0-17). Overall, a significantly longer interval between randomization and treatment was noted with clipping (mean 1.7 versus 1.1 days; $p<0.0001$), in which respectively 17 patients died following a re-bleed vs. 6 in the endovascular arm (RR=2.81; 95%CI 1.11-7.11). Additional analysis of this treatment delay showed a significant difference between UK and non-UK centers (mean 1.4 versus 0.4 days — $p<0.0001$). In non-UK centers, 3/499 rebleeds were observed, versus 47/1644 in the UK. All pre-treatment deaths occurred in UK centers. Median time from SAH to admission was 0 days (IQR 0-1), balanced between two arms. Median time from admission to randomization was 1 day (IQR 1-3).

Table 1 | Baseline patient characteristics of the patients after exclusion of pre-treatment deaths (n=27).

Number (%)	Endovascular treatment n=1065	Neurosurgical treatment n=1051
Male sex	395 (37)	392 (37)
Median age (IQR)	52 (44 - 60)	52 (44 - 60)
WFNS grade at randomization		
1	671 (63)	654 (63)
2	268 (25)	273 (26)
3	65 (6)	67 (6)
4	37 (4)	33 (3)
5	9 (1)	9 (1)
Not assessable	15 (1)	15 (1)
Lumen size		
≤5	550 (52)	566 (54)
6-10	433 (40)	416 (39)
≥11	82 (8)	69(7)
Aneurysm location		
Anterior cerebral artery	536 (51)	535 (51)
Internal carotid artery	344 (32)	344 (33)
Middle cerebral artery	161 (15)	138 (14)
Posterior circulation	24 (2)	34 (3)
Fisher grade		
0	10 (1)	4 (1)
1	48 (5)	66 (6)
2	188 (18)	169 (16)
3	449 (42)	446 (42)
4	370 (34)	366 (35)

IQR = interquartile range

Figure 1 | Flowchart of randomization to actual treatment.

ITT=intention to treat; EVT=endovascular treatment; NST=neurosurgical treatment

Table 2 | Relative risk (95% CI) of death or dependency and death alone, for endovascular coiling compared to neurosurgical clipping, at 1 year and 5 years, for the original ITT analyses and the 4 additional analyses. Bold indicates statistical significance.

Type of analysis	1 year		5 years	
	Death or dependency	Death	Death or dependency	Death
Original ITT-analysis	0.76 (0.66-0.88)	0.81 (0.61-1.06)	0.85 (0.76-0.99)	0.78 (0.62-0.98)
After exclusion of all pre-treatment deaths	0.77 (0.67-0.89)	0.88 (0.66-1.19)	0.88 (0.77-1.02)	0.82 (0.64-1.05)
After exclusion of all pre-treatment rebleedings	0.77 (0.67-0.90)	0.89 (0.66-1.20)	0.88 (0.77-1.02)	0.82 (0.64-1.05)
As-treated analysis	0.80 (0.69-0.92)	0.87 (0.64-1.16)	0.90 (0.78-1.03)	0.85 (0.66-1.08)
Good-grade patients, as-treated analysis	0.73 (0.62-0.87)	0.74 (0.52-1.06)	0.82 (0.71-0.96)	0.72 (0.54-0.97)

ITT=Intention To Treat

Figure 2 | Kaplan-Meier graph of cumulative percentage of mortality after exclusion of pre-treatment deaths. Patients are followed-up for a minimum of 5 and maximum of 14 years.

DISCUSSION

This study aims to investigate the effect of treatment delay on the ISAT-outcomes. These analyses support the conclusion of ISAT that at 1-year after aSAH, coiling had a better outcome. After 5 years, with pre-treatment deaths excluded, the difference between coiling and clipping did not reach significance. The most dreaded complication of aSAH is early rebleeding, which is often lethal. In ISAT, 50 patients suffered from a rebleeding before treatment. It is likely that the interval between randomization and treatment played a significant role. This is further supported by the absence of pretreatment deaths in the non-UK cohort, as treatment was initiated faster than in UK centers.

Poor-grade patients more often receive delayed treatment and have a worse clinical outcome due to the primary hemorrhage. In line with this, a Cochrane review on coiling versus clipping emphasized that the original ISAT results applied primarily for good-grade patients, and that for poor-grade patients the favorability of coiling is not well established.¹⁶ Currently, ISAT II is ongoing, including patients not originally recruited in ISAT, mainly focusing on poor-grade patients or patients in whom clipping was considered

a better alternative. The interim results show that at 1 year 16/42 (38%) and 10/34 (29%) patients were dead or dependent in the surgical and endovascular allocations respectively, but with wide confidence intervals.¹⁷

It is important to recognize that the originally applied ITT analysis is considered the gold standard when comparing two types of treatment.¹⁸ However, current CONSORT-guidelines recommend that also other relevant analyses should be reported if underestimation of treatment effect is expected. The additional analyses allow for a wider understanding of ISAT, which is important as the main evidence on supremacy of coiling is originating from ISAT.¹⁶

In addition to ISAT, three other (substantially smaller) randomized trials made a direct comparison between endovascular coiling and neurosurgical clipping. One of these trials was not published.^{19,20} Koivisto et al. randomized 109 patients and concluded that coiling and clipping were comparable after one year.²¹ The pre-randomization design of the BRAT-trial included 471 patients and showed a significant better outcome at one-year follow-up for endovascularly treated patients.²⁰ At three years, the advantage of endovascular coiling over neurosurgical clipping had disappeared.^{22,23} However, the methodological design of this trial is questionable, allocation was by day of admission and thus unconcealed and also patients with non-saccular aneurysms were included. Furthermore, the study was underpowered to look at any sub-groups and had significant amount of missing data at follow-up. As such, it is hard to draw definitive conclusions from this data. Apart from these trials, only observational studies have been performed, most of them examining subgroups of aSAH patients.²⁴

Some limitations need to be addressed. Given the retrospective design, the reasons of treatment delay in individual patients was not identified. Furthermore, it is likely that results of endovascular treatment have substantially improved over the last decades, due to better techniques, better quality of angiographic imaging and increased experience of physicians.²⁵⁻²⁷ Also other changes in treatment of SAH patients occurred, e.g. blood-pressure management. Because of these changes over time, the results from ISAT do likely not reflect current clinical outcomes. Three recent prospective RCTs compared different coil types, providing reliable prospective data on contemporary clinical outcome of coiling in good-grade patients.²⁸⁻³⁰

What these additional analyses do show however, and makes it still very timely, is that the outcome of neurosurgical clipping as demonstrated in the original ITT analysis was negatively impacted by the higher number of early rebleeds in the clipping arm, because of

a delay between randomization and initiation of treatment. This implies that it is probably not justified to delay the securing of a ruptured aneurysm if either endovascular coiling or neurosurgical clipping are not readily available because of logistic issues, and the patient is considered a suitable candidate for both treatment modalities. For example, patients in good clinical condition with middle cerebral artery (MCA) aneurysms.

It has been shown that rebleeding of the aneurysm occurs most frequently in the first 24 hours after ictus and recent data suggest that this may be highest in the first 12 hours.⁶ Ultra-early aneurysm treatment was advocated, preferably in the first 24 hours, to prevent this often-fatal complication, in patients considered to be at high risk for rebleeding. It is specifically this patient population (at a high risk of a rebleeding), where patients may not be in a good clinical condition on admission and need neurological resuscitation first, e.g. placement of an external ventricular drain. Still, in these patients, aneurysm treatment is not yet regarded a medical emergency everywhere.^{7,8} The results of this study further highlight the importance of aneurysm treatment on an urgent basis to prevent early rebleeding, especially in those considered at highest risk.⁶

Conclusions

These additional analyses support the conclusion of ISAT that at 1-year follow-up after aneurysmal subarachnoid hemorrhage endovascular coiling leads to a better outcome than neurosurgical clipping. However, after correcting for treatment delay, this difference has diminished at 5-year follow-up. The higher number of pre-treatment deaths in the neurosurgical group due to a delay in treatment initiation, highlights the importance of aneurysm treatment on an urgent basis to prevent early rebleeding.

REFERENCES

1. Molyneux AJ, Kerr RS, Yu LM, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomized trial. *Lancet* 2002; 360: 1267–74.
2. Molyneux A, Kerr RS, Yu L-M, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized comparison of effects on survival, dependency, seizures, rebleeding, subgroups. *Lancet* 2005; 6736: 809–17.
3. Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid hemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009; 8: 427–33.
4. Molyneux AJ, Birks J, Clarke A, et al. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet* 2015; 385: 691–7.
5. Gnanalingham KK, Apostolopoulos V, Barazi S, et al. The impact of the international subarachnoid aneurysm trial (ISAT) on the management of aneurysmal subarachnoid hemorrhage in a neurosurgical unit in the UK. *Clin Neurol Neurosurg* 2006; 108: 117–23.
6. van Donkelaar CE, Bakker NA, Veeger NJGM, et al. Predictive Factors for Rebleeding After Aneurysmal Subarachnoid Hemorrhage. *Stroke* 2015; 46: 2100–6.
7. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage. *Cerebrovasc Dis* 2013; 35: 93–112.
8. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2012; 43: 1711–37.
9. Tait MJ, Critchley GR, Norris JS. How much can be concluded from the International Subarachnoid Aneurysm Trial (ISAT)? *Br J Neurosurg* 2007; 21: 3–6.
10. Bakker NA, Metzemaekers JDM, Groen RJM, et al. International subarachnoid aneurysm trial 2009: Endovascular coiling of ruptured intracranial aneurysms has no significant advantage over neurosurgical clipping. *Neurosurgery* 2010; 66: 961–2.
11. Thomas AJ, Ogilvy CS. ISAT: Equipoise in treatment of ruptured cerebral aneurysms? *Lancet* 2015; 385: 666–8.
12. Bakker NA, van Dijk JMC, Veeger NJGM. ISAT: End of the debate on coiling versus clipping? *Lancet* 2015; 385: 2250–1.
13. Molyneux AJ, Birks J, Kerr RS. ISAT: End of the debate on coiling versus clipping? *Lancet* 2015; 385: 2250–1.
14. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. *PLoS Med* 2010; 7: 1–7.

15. Van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19: 604–7.
16. Lindgren A, Vergouwen M, Van Der Schaaf I, et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid hemorrhage (Review). *Cochrane Database Syst Rev* 2018; 8: CD003085.
17. Darsaut TE, Roy D, Weill A. A randomized trial of endovascular versus surgical management of ruptured intracranial aneurysms: Interim results from ISAT2. *Neurochirurgie*. 2019;65:370-376
18. Sheiner LB. Is intent-to-treat analysis always (ever) enough? *Br J Clin Pharmacol* 2002; 54: 203–11.
19. Van Der Schaaf I, Algra A, Wermer M, et al. Endovascular coiling versus neurosurgical clipping for patients with aneurysmal subarachnoid hemorrhage. - PubMed - NCBI. *Cochrane Database Syst Rev* 2009;10–2.
20. McDougall CG, Spetzler RF, Zabramski JM, et al. The barrow ruptured aneurysm trial: Clinical article. *J Neurosurg* 2012; 116: 135–44.
21. Koivisto T, Vanninen R, Hurskainen H, et al. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. *Stroke* 2000; 31: 2369–77.
22. Spetzler RF, McDougall CG, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial: 3-year results. *J Neurosurg* 2013; 119: 146–57.
23. Spetzler RF, McDougall CG, Zabramski JM, et al. The Barrow Ruptured Aneurysm Trial: 6-year results. *J Neurosurg* 2015; 123: 609–17.
24. Li H, Pan R, Wang H, et al. Clipping versus coiling for ruptured intracranial aneurysms: A systematic review and meta-analysis. *Stroke* 2013; 44: 29–37.
25. Molyneux AJ. Changes in the treatment of patients with subarachnoid hemorrhage following publication of the International Subarachnoid Aneurysm Trial. *Clin Neurol Neurosurg* 2006; 108: 115–6.
26. Lin N, Cahill KS, Frerichs KU, et al. Treatment of ruptured and unruptured cerebral aneurysms in the USA: A paradigm shift. *J Neurointerv Surg* 2012; 4: 182–9.
27. Alshafai N, Cusimano MD FO. Global differences in the present and future management of cerebral aneurysms. *World Neurosurg* 2013; 80: 717–22.
28. White PM, Lewis SC, Gholkar A, et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomized controlled trial. *Lancet* 2011; 377: 1655–62
29. McDougall CG, Johnston SC, Gholkar A, et al. Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial. *AM J Neuroradiol*. 2014; 35: 935-42
30. Coley S, Sneade M, Clarke A, et al. Cerecyte Coil Trial: Procedural Safety and Clinical Outcomes in Patients with Ruptured and Unruptured Intracranial Aneurysms. *AM J Neuroradiol*. 2012; 33: 474-480

SUPPLEMENTAL TABLES

Table 1 | Distribution of functional outcomes according to the modified Rankin Scale (mRS), after exclusion of pre-treatment deaths, and after exclusion of pre-treatment rebleedings.

Functional outcome (mRS)	Exclusion of pre-treatment deaths*			Exclusion of pre-treatment rebleeds**		
	1 year EVT n=1065	NST n=1051	5 years EVT n=1065	1 year EVT n=1054	NST n=1039	5 years EVT n=1054 NST n=1039
0	260 (24)	187 (18)	274 (25)	259 (25)	187 (18)	273 (26)
1	301 (28)	292 (28)	226 (21)	298 (28)	289 (28)	224 (21)
2	252 (24)	250 (24)	149 (14)	251 (24)	249 (24)	147 (14)
Total	813 (76)	729 (70)	649 (60)	808 (77)	725 (70)	644 (61)
3	107 (10)	141 (13)	88 (8)	105 (10)	140 (13)	86 (8)
4	30 (3)	42 (4)	26 (3)	30 (3)	41 (4)	26 (3)
5	28 (3)	38 (4)	24 (2)	26 (2)	35 (4)	23 (2)
6 (death)	77 (7)	86 (8)	104 (11)	75 (7)	83 (8)	102 (10)
Total	242 (23)	307 (29)	242 (23)	236 (22)	299 (29)	237 (23)
Missing, n (%)	10 (1)	15 (1)	174 (16)	10 (1)	15 (1)	173 (16)

EVT=endovascular treatment; NST=neurosurgical treatment; *8 in the EVT arm; 19 in the NST arm; * 19 in the EVT arm; 31 in the NST arm

Table II | Distribution of functional outcomes according to the modified Rankin Scale (mRS), as-treated analysis, and as-treated analysis of good-grade patients.

Functional outcome (mRS)	As-treated analysis*				Good-grade patients, as-treated**			
	1 year EVT n=1091	NST n=1018	5 years EVT n=1091	NST n=1018	1 year EVT n=964	NST n=897	5 years EVT n=964	NST n=897
0	262 (24)	184 (18)	281 (26)	195 (19)	248 (26)	175 (20)	273 (28)	185 (21)
1	308 (28)	284 (28)	232 (21)	212 (21)	284 (29)	264 (29)	211 (22)	195 (22)
2	260 (24)	242 (24)	153 (14)	174 (17)	238 (25)	213 (24)	139 (14)	156 (17)
Total	830 (76)	710 (70)	666 (61)	581 (57)	770 (80)	652 (73)	623 (64)	536 (60)
3	109 (10)	136 (13)	89 (8)	95 (9)	92 (10)	108 (12)	75 (8)	81 (9)
4	32 (3)	40 (4)	26 (2)	20 (2)	22 (2)	35 (4)	21 (2)	18 (2)
5	32 (3)	33 (3)	27 (3)	15 (2)	20 (2)	27 (3)	17 (2)	11 (1)
6 (death)	78 (7)	84 (8)	108 (10)	119 (12)	50 (5)	63 (7)	74 (8)	94 (10)
Total	251 (23)	293 (28)	250 (23)	249 (25)	184 (19)	233 (26)	187 (20)	204 (22)
Missing, n (%)	10 (1)	15 (2)	175 (16)	188 (18)	10 (1)	12 (1)	154 (16)	157 (18)

EVT=endovascular treatment; NST=neurosurgical treatment; * actual treatment received omitting those who received no treatment; ** WFNS I-II at randomization

Table III | Baseline patient characteristics of the patients after exclusion of pre-treatment rebleedings (n=50).

Number (%)	Endovascular treatment n=1054	Neurosurgical treatment n=1039
Male sex	389 (37)	385 (37)
Median age (IQR)	52 (44 - 60)	52 (44 - 60)
WFNS grade at randomization		
1	665 (63)	649 (62)
2	265 (25)	268 (26)
3	64 (6)	65 (6)
4	36 (3)	33 (3)
5	9 (1)	8 (1)
Not assessable	15 (1)	16 (1)
Lumen size		
≤5	547 (52)	561 (54)
6-10	426 (40)	412 (40)
≥11	81 (8)	66 (6)
Aneurysm location		
Anterior cerebral artery	528 (51)	527 (51)
Internal carotid artery	341 (32)	341 (33)
Middle cerebral artery	161 (15)	138 (13)
Posterior circulation	24 (2)	33 (3)
Fisher grade		
0	10 (1)	4 (1)
1	47 (4)	66 (6)
2	185 (18)	167 (16)
3	444 (42)	442 (42)
4	368 (35)	360 (35)

IQR = interquartile range

Table IV | Baseline patient characteristics of the patients with actual treatment received.

Number (%)	Endovascular treatment n=1091	Neurosurgical treatment n=1018
Male sex	408 (37)	377 (37)
Median age (IQR)	52 (44 - 59)	52 (43 - 60)
WFNS grade at randomization		
1	690 (63)	631 (62)
2	274 (25)	266 (26)
3	65 (6)	66 (6)
4	39 (4)	30 (3)
5	10 (1)	8 (1)
Not assessable	13 (1)	17 (2)
Lumen size		
≤5	564 (52)	547 (54)
6-10	439 (40)	408 (40)
≥11	88 (8)	63 (6)
Aneurysm location		
Anterior cerebral artery	553 (51)	513 (50)
Internal carotid artery	353 (32)	334 (33)
Middle cerebral artery	158 (15)	141 (14)
Posterior circulation	27 (2)	30 (3)
Fisher grade		
0	10 (1)	4 (1)
1	50 (5)	64 (6)
2	195 (18)	162 (16)
3	462 (42)	430 (42)
4	374 (34)	358 (35)

IQR = interquartile range

Table V | Baseline patient characteristics of the good-graded patients with actual treatment received.

Number (%)	Endovascular treatment n=964	Neurosurgical treatment n=897
Male sex	364 (37)	332 (38)
Median age (IQR)	51 (43 - 59)	52 (43 - 59)
WFNS grade at randomization		
1	690 (63)	631 (62)
2	274 (25)	266 (26)
Lumen size		
≤5	508 (53)	493 (55)
6-10	387 (40)	351 (39)
≥11	69 (7)	53 (6)
Aneurysm location		
Anterior cerebral artery	490 (51)	457 (51)
Internal carotid artery	317 (33)	295 (33)
Middle cerebral artery	133 (14)	120 (13)
Posterior circulation	24 (2)	25 (3)
Fisher grade		
0	10 (1)	4 (1)
1	47 (5)	63 (7)
2	189 (20)	156 (17)
3	432 (44)	394 (44)
4	286 (30)	280 (31)

IQR = interquartile range

Chapter 7.

General discussion and future directions

Spontaneous subarachnoid hemorrhage is a devastating type of stroke, with the most frequent cause being a ruptured intracranial aneurysm. Although case-fatality rates of patients with SAH have decreased over the past decades due to improvements in diagnostics and treatment, mortality and morbidity rates remain high. Aim of this thesis was to gain more insight in predictive factors for aneurysm rupture and its subsequent rebleeding, as well as for the patients' outcome after SAH. In this chapter, the results of the previous chapters are summarized and put into the perspective of clinical practice. Finally, future directions are put forward.

Aneurysm rupture

The exact underlying pathophysiology of aneurysm formation and rupture, the latter resulting in a SAH, remains elusive. As part of the attempt to unravel the underlying mechanisms, the seasonal variation of SAH has been extensively studied. In chapter 2, we reviewed the seasonal incidence of SAH in the northern region of the Netherlands, and found that atmospheric pressure variations were related to an increased incidence of aSAH. Furthermore, significantly less aneurysmal SAH's occur in July, consistent with previous studies.¹ Although the clinical implications of these findings are limited, they can be indicative to further elucidate the pathophysiology of aneurysm rupture.

One of the most promising directions of research regarding aneurysm rupture is the role of inflammation. It becomes increasingly clear that chronic inflammation predetermines aneurysm wall degeneration which can lead to unstable aneurysms.²⁻⁴ Increased hemodynamic stress initiates this inflammatory process leading to a complex cascade involving cytokines and proteinases, and results in degradation of extracellular matrix and apoptosis of smooth muscle cells in the arterial wall.³ One of the hypotheses mentioned in chapter 2 is that meteorological factors trigger the chronic inflammatory process in the aneurysm wall after which the rupture occurs.

In recent years, the prevalence of intracranial aneurysms has increased due to more frequent use of cranial imaging, as well as the improvement of these imaging techniques. Most of these aneurysms do not rupture, but it remains difficult to differentiate between stable and unstable aneurysms. This creates a precarious dilemma for patients harboring an unruptured intracranial aneurysm. Treatment by either coiling or clipping is accompanied by significant risks and complications, with treatment-related mortality and morbidity up to 5%.⁵ Conservative treatment on the other hand cannot exclude the risk of a potential lethal SAH, so strict follow-up with cranial imaging is advised. Although several prediction models for aneurysm growth and rupture are developed based on well-known risk factors,⁶⁻⁸ they are not completely accurate. Therefore, there is an on-going search for new

diagnostics to determine the stability of intracranial aneurysms, in order to treat instable aneurysms timely. Promising are the new imaging techniques focusing on visualization of inflammation of the aneurysm wall, such as gadolinium-enhancement on the MRI.⁹

Risk for rebleeding and early aneurysm treatment

After aneurysmal SAH, rebleeding is one of the most feared complications and therefore the aneurysm should be occluded by either endovascular or neurosurgical treatment. The European Stroke Organization and the American Stroke Association guidelines recommend aneurysm occlusion as soon as logistically feasible, and preferably <72h after ictus.¹⁰⁻¹¹ This guideline is subject to broad interpretation, and no consensus exists about the exact preferred timing of aneurysm occlusion. There is increasing evidence that early treatment, <24 hours after ictus, is beneficial for both reducing the risk for rebleeding and improving outcome after SAH.¹²⁻¹⁵ Nevertheless, as shown in chapter 3, most rebleeds occur within the first 8 hours after the ictus, so for prevention of these rebleeds, an ultra-early emergency treatment (preferably <8 hours) should be applied rather than 'early' treatment <24 hours.

In chapter 3, we identified risk factors for the occurrence of early rebleeding in relation to the time. Our results show that patients with mFisher grade 3-4 have a four-time increased risk for rebleeding compared to patients with a low mFisher grade. As noted in chapter 3, we speculate that the amount of blood is a surrogate marker of the defect size and stability of the ruptured aneurysm wall, irrespective of the patient's clinical condition, as the latter was not associated with rebleeding.

Furthermore, the initiation of CSF-drainage was also independently associated with rebleeding, which could be explained by the sudden decrease of cerebrospinal fluid pressure affecting the transluminal pressure over the ruptured aneurysm wall. The association between rebleeding and CSF-drainage has been described before, including a recent large meta-analysis by Cagnazzo et al.¹⁶ In this meta-analysis, they included a total of 6804 patients from 16 studies, and found that rebleeding occurred in 18.8% of patients after EVD placement, versus in 6.4% of patients without EVD (OR 3.9, $p < 0.001$). The mean time between EVD insertion and rebleeding was 1 hour with a range of 0-8 hours, which is consistent with our findings. Of interest, in a study investigating the amount of CSF-drainage in relation to rebleeding, it was found that the volume of CSF-drainage was highly correlated with the probability of in-hospital rebleeding.¹⁷ Although a causal relationship is still difficult to prove, these results strengthen the conclusion that rebleeding is related to CSF-drainage.

In view of these results, the timing of treatment of patients at high risk for rebleeding should be reconsidered. Nowadays, patients in a good clinical condition should be treated 'as soon

as possible', but at least within 72 hours. In my opinion, the patients with a mFisher grade 3-4 in a good clinical condition on admission (WFNS I-III), should be regarded as a medical emergency requiring ultra-early aneurysm treatment. Furthermore, if in these patients CSF-drainage is deemed necessary, aneurysm occlusion should be performed directly afterwards the placement of the drain, to reduce the additional chance of rebleeding in that time window. Especially for patients who will be treated by clipping, this time could easily be minimized when placement of the drain is performed during the clipping procedure.

For patients in a poor clinical condition, however, treatment nowadays is different. These patients are first neurologically resuscitated, and afterwards the clinical condition is observed. Only in case of improvement, the patients would receive aneurysm treatment. As one obviously want to avoid emergency aneurysm treatment in comatose patients who would likely not recover well, I think that patients with a mFisher grade 3-4 and a poor clinical condition on admission (WFNS IV-V), should receive a secondary assessment after neurological resuscitation. Then, it can be decided whether or not they should receive emergency treatment. For this secondary assessment, the SAFIRE grading-scale could be used for accurate identification of true poor-grade patients. This proposed new treatment paradigm of patients with an aneurysmal SAH is visualized in Figure 1.

The implementation of emergency treatment for a subgroup of SAH patients would mean the availability of treatment 24 hours per day and 7 days per week for both modalities. Recent changes in the treatment of ischemic stroke already proved the achievability of this. Here, it also has become apparent that immediate endovascular intervention (<6h) is beneficial in patients with a proximal arterial occlusion in the anterior cerebral circulation¹⁸, resulting in the availability of this treatment 24/7, also during the night. The proposed emergency treatment in patients with aSAH would therefore be in line with the successfully adopted 'time-is-brain' concept in the treatment of ischemic stroke.

Obviously, the implementation of a 24-hours emergency protocol raises the question whether the inevitable avoidance of rebleedings is also associated with improved clinical outcome. A potential disadvantage of emergency treatment, could be an increase in treatment-related complications. Performance of procedures at night when circumstances are less optimal, for instance due a less experienced team, could attribute to this. Although Park et al. showed in their cohort study that it is likely that the number of poor outcomes would decline after implementation of an emergency protocol¹², a randomized controlled trial comparing 24-hours emergency treatment versus conventional treatment for high risk patients would be needed to unequivocally answer this question.

Figure 1 | Proposed treatment paradigm of aSAH in the acute phase.
 mFisher=modified Fisher grade, SAH=subarachnoid hemorrhage, SAFIRE=SAFIRE grading scale (see chapter 5), WFNS=World Federation of Neurosurgical Societies grading scale, CSF=cerebrospinal fluid

The improvements in clinical outcome would also depend on the number of preventable rebleedings, and with that the number of preventable poor outcomes due to rebleeding. In chapter 3, we determined “preventable rebleedings” as rebleedings >3 hours after the ictus. It must be acknowledged that this is an ambitious timeframe which would not always be achieved in clinical practice. A Dutch study by Germans et al. investigated time intervals from initial presentation of SAH to diagnosis and subsequent treatment. In their area with relatively short referral distances, median time from presentation to diagnosis was 169 minutes and median time from diagnosis to treating center was an additional 114 minutes.¹⁹ Thus, to achieve ultra-early treatment of aneurysms, large improvements in logistics and awareness should be made. Interestingly, in an other study performed by Germans et al., they found that a majority of the rebleedings in their population (60%) occurred after arrival at the treating center.²⁰ This suggests that although referral times might be longer than 3 hours, improvements in logistics within neurovascular treating centers can already contribute to a rapid decline of the number of early rebleedings.

It is important to recognize that in countries with larger referral area's, the number of preventable rebleedings might be substantial lower. A recent American study by Linzey et al., retrospectively analyzed how many rebleedings could have been prevented in their entire aSAH population by a 24-hours emergency treatment protocol. They found that only 4.2% of the rebleedings could have been prevented, because the majority of the rebleedings occurred before admission to the treating institute.²¹ Hence despite efforts to shorten time to treatment, ultra-early rebleedings will still occur, especially when arrival times are longer.

There are suggestions that for such 'unpreventable' ultra-early rebleedings, short-term administration of antifibrinolytic agents such as tranexamic acid might be effective²², which can be administered directly after the diagnosis of aSAH and before a possible transfer to a neurovascular treating center. The benefit of antifibrinolytic agents for prevention of rebleeding is shown before, however, the long-term administration of these agents increased the risk of ischemic infarctions significantly.²³ Recently, Post et al. performed an retrospective, multicenter comparison study in which two treatment protocols were compared; one group of patients received standard care, the other group received short-term administration of tranexamic acid in addition.²⁴ Although there was a significant decline in in-hospital mortality, rebleeding rates did not differ and poor outcome appeared to be even higher in the group of patients treated with tranexamic acid. For conclusive evidence, the results of the ULTRA-trial are awaited, a randomized controlled trial investigating whether early and short-time administration of tranexamic acid decreases rebleeding and, most important, improves outcome.²⁵ But for now, tranexamic acid does not have a place in treatment of SAH patients, and emergency aneurysm occlusion for high-risk patients seems the most effective approach to decline rebleeding rates in aSAH patients.

Prediction of outcome

As mentioned before, accurate prediction of outcome is important as aneurysm repair is sometimes delayed or withheld because treatment is seen as futile, whereas patients might actually have a reasonable chance of a good outcome. Withholding them from aneurysm repair is keeping them at risk for aneurysm rebleeding. Nowadays, the golden standard for prediction of outcome is the WFNS grade on admission to the hospital, but it is known that many of the patients with a WFNS grade 4-5 recover without large disabilities.

As shown chapter 4 and 5, there are two important findings concerning prediction of outcome. First, the rWFNS grade, assessed after neurological resuscitation, identifies

poor-graded patients more accurately compared to the WFNS grade assessed on admission. Second, although the rWFNS is the strongest predictor for outcome after SAH, the addition of age, aneurysm size and Fisher grade provides a more accurate prediction of outcome (mRS). The final prediction model performed well in other cohorts, and the derived SAFIRE grading scale is a valid instrument to predict outcome in terms of mRS.

With the SAFIRE grading scale, we predict the chance of good versus poor outcome of patients using the mRS scale as outcome measure. Although this is a well validated scale and the golden standard in stroke studies²⁶, it is important to note that the mRS scale focuses only on physical disability while neuropsychological factors such as cognitive deficits and mental fatigue or non-ability to return to work are not taken into account.^{27,28} Neuropsychological factors are largely understated in studies concerning outcome after aSAH, but as more people survive with a 'good outcome' over the last years, this becomes increasingly important. We did not investigate these endpoints in our studies, so it is important to recognize the limitation of the SAFIRE grading-scale in prediction of more specific fields of functioning after aSAH.

In addition, it is important to note that prediction models in general are tools for physicians to balance out decisions regarding treatment and are no strict guidelines for, for instance, withdrawal of care. Obviously, the decision to withdraw care is not a decision only made by the treating physician, but always in collaboration with the patient's family. In general, family will balance out the presumed patient's desires with the potential neurological outcome, in which they will rely on the medical expertise of the treating physician. Therefore, it is important that physicians have reliable tools to support the process of clinical decision-making for the benefit of their patients.

Type of aneurysm treatment

The ISAT trial is the largest and most impactful trial comparing the effect of endovascular coiling versus neurosurgical clipping, with first results published in 2002. Before ISAT, two considerably smaller randomized trials (Brilstra et al.²⁹ and Koivisto et al.³⁰) were performed, including only 20 and 107 patients respectively. Following ISAT, no other large randomized controlled trial concerning this subject was performed, so the perceived evidence regarding the benefit of coiling over clipping originates from ISAT. After the publication of ISAT, a major shift in treatment did occur, with most patients now being treated endovascularly, indicating the great impact of this trial. However, the results of ISAT were extrapolated towards all patients with aSAH, while the included patient population in ISAT was highly homogenous (mostly good-graded patients harboring small anterior aneurysms).

Another point of criticism was that in ISAT significantly more patients in the neurosurgical group died before treatment could be effected, compared to the endovascular group.³¹ As shown in chapter 6, it is likely that the explanation for this difference is the significantly longer time between randomization and treatment in this particular group, which led to more rebleeds. The results of chapter 6 support the conclusion of ISAT that at 1-year follow-up after aSAH, endovascular coiling leads to a better outcome than neurosurgical clipping, however, at 5-year follow-up this difference in outcome has disappeared. In short, when correcting for treatment delay, coiling and clipping can be considered comparable in long-term based on the data and endpoints of ISAT.

In chapter 6, we also showed that for good-grade patients, the favorability of coiling in long term remained. ISAT included mainly good-grade patients, which was also highlighted again by a recently published Cochrane review comparing coiling and clipping.²⁹ In that review, the authors emphasized that the original ISAT results apply primarily for good-grade patients. For poor-grade patients, the favorability of coiling is not well established. Further research concerning preferred type of aneurysm treatment in poor-graded patients is therefore warranted. Currently the inclusion of ISAT II is running, a trial comparing coiling and clipping in a population of patients not originally included in ISAT.³² In the recently published interim results, the primary outcome (death or dependency at one-year) was available for 76 patients. Of these patients, 16/42 (38%) and 10/34 (29%) patients had reached the composite endpoint of dead or dependent at one-year in the surgical and endovascular allocations respectively, but with wide confidence intervals.³³ The trial is continuing to recruit and has enrolled about 160 patients in 6 centers.

The results of chapter 6 underline the nuances in the interpretation of the ISAT results and highlight the importance of early aneurysm repair for the prevention of early rebleeding. After the correction for treatment delay in ISAT, the treatment modalities give comparable outcomes on the long term. This implies that it is probably not justified to delay the securing of a ruptured aneurysm if either endovascular coiling or neurosurgical clipping are not readily available because of logistic issues, and the patient is considered a suitable candidate for both treatment modalities.

As mentioned before, a major limitation of many studies comparing outcome of the two treatment modalities, including ISAT, is the lack of neuropsychological endpoints. Therefore, there is little knowledge concerning the impact of the type of treatment on neuropsychological and cognitive functioning. The present evidence is originating from small studies, but these show no large differences between the modalities except for a few fields as executive function and verbal memory.^{34,35} In these areas that are considered

to be the more complex neurocognitive fields, coiling tends to outperform clipping. No randomized controlled trial concerning this subject is performed, so in these studies inequalities in baseline characteristics might be present. Possibly, the surgical manipulation during the clipping procedure causes additional/new structural damage to the already vulnerable brain, resulting in more severe deficit in cognitive functioning when compared to patients after endovascular aneurysm repair. More research regarding this subject is warranted to provide conclusive evidence.

Future perspectives

Following our findings and the discussion hereinabove, I would like to put forward some recommendations for future research. Regarding unruptured aneurysms, future studies should focus on new diagnostic tools for the prediction of an aneurysm rupture. Inflammation seems a key-process in the growth and rupture process of aneurysms, so new diagnostics visualizing inflammation in the aneurysm wall may be promising to improve identification of patients who need aneurysm treatment. With this, it might be possible to develop more accurate prediction models for aneurysm rupture.

In respect of the proposed change in treatment paradigm for patients at high risk for rebleeding, we should investigate the amount of preventable rebleedings after implementation of such protocol. When this treatment turns out to be beneficial, it would be interesting to investigate if other aSAH patients would benefit from emergency treatment. Especially for the patients in a good clinical condition this might be the case, as the loss of (quality of) life due to rebleeding is extremely high and the condition of the patient allows fast treatment. When investigating the benefit of emergency treatment for patients at high risk for rebleeding, it would be interesting to compare the patients treated by ultra-early coiling and clipping, as both treatments are accompanied by disadvantages and possible complications related to ultra-early treatment. For neurosurgical treatment, this is mostly due to edema of the brain tissue in early stage after aSAH. For endovascular treatment the risk of per-procedural rebleeding appears to be higher when treatment occurs in the first hours (<6h) after aSAH.³⁶

Considering treatment of poor-grade patients, future studies should focus on the optimal timing of treatment and preferred treatment modality. Based on retrospective studies, there is conflicting evidence whether treatment within <24h in these patients will actually improve outcome^{37,38}, but a randomized controlled trial concerning this question, the TOPSAT II trial, is underway.³⁹ An interesting subgroup of poor-grade patients are patients with a space-occupying intracerebral hematoma due to aneurysm rupture, most often originating from the middle cerebral artery. In these patients, preferred treatment strongly

differs among neurovascular centers. In some centers they prefer to coil first, after which the intracerebral clot will be surgically removed. In other centers, they combine surgical evacuation of the hematoma with clipping. Several other factors may determine preferred treatment and potential outcome, such as volume and location of the hematoma, which should be considered when investigating optimal treatment for these patients. Further validation of the SAFIRE grading scale in other cohorts is also encouraged, to establish an optimal prediction model with broad support throughout the neurovascular community.

Conclusions

The thesis shed light on the seasonal incidence of SAH and the relationship with meteorological factors. Furthermore, it aids to the prediction of rebleeding and short-term outcome after SAH. Based on this thesis, a new treatment paradigm for the acute phase of SAH is proposed, recommending treatment of patients at high risk for rebleeding on an emergency base. Furthermore, this thesis highlights the importance of accurate identification of patients in a poor clinical condition for decisions regarding (timing of) treatment. The SAFIRE grading scale is proposed as a new tool to assess the patients' outcome soon after the ictus. Last, it revealed the impact of treatment delay and rebleeding on the outcomes of ISAT, and found that after correcting for this, coiling and clipping could be considered comparable in long term based on ISAT data. All together, these new insights can lead to improved treatment of patients with SAH and a further decline in mortality and morbidity rates.

REFERENCES

1. De Steenhuijsen Piters WAA, Algra A, Van Den Broek MFM, Dorhout Mees SM, Rinkel GJE. Seasonal and meteorological determinants of aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *J Neurol*. 2013; 260:614–9.
2. Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, et al. Biology of intracranial aneurysms: Role of inflammation. *J Cereb Blood Flow Metab*. 2012; 32:1659–76.
3. Chalouhi N, Hoh BL, Hasan D. Review of Cerebral Aneurysm Formation, Growth, and Rupture. *Stroke* 2013; 44:3613–22.
4. Tulamo R, Frösen J, Hernesniemi J, Niemelä M. Inflammatory changes in the aneurysm wall: a review. *J Neurointerv Surg*. 2018; 10:58–67.
5. Naggara O, White P, Guilbert F, Roy D, Weill A, Raymond J. Endovascular Treatment of Intracranial Unruptured Aneurysms: Systematic Review and Meta-Analysis of the Literature on Safety and Efficacy. *Radiology*. 2010; 256:887–97.
6. Greving JP, Wermer MJH, Brown RD, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: A pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014; 13:59–66.
7. Backes D, Vergouwen MDI, Tiel Groenestege AT, et al. PHASES Score for Prediction of Intracranial Aneurysm Growth. *Stroke*. 2015; 46:1221–6.
8. Backes D, Rinkel GJE, Greving JP, et al. ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms. *Neurology*. 2017; 88:1600–6.
9. Vergouwen MDI, Backes D, van der Schaaf IC et al. Gadolinium Enhancement of the Aneurysm Wall in Unruptured Intracranial Aneurysms Is Associated with an Increased Risk of Aneurysm Instability: A Follow-Up Study. *AJNR* 2019; 40:1112–1116
10. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage. *Cerebrovasc Dis* 2013; 35: 93–112.
11. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2012; 43:1711–37.
12. Park J, Woo H, Kang DH, et al. Formal protocol for emergency treatment of ruptured intracranial aneurysms to reduce in-hospital rebleeding and improve clinical outcomes. *J Neurosurg*. 2015; 122:383–91.
13. Wong GKC, Boet R, Ng SCP, et al. Ultra-early (within 24 Hours) aneurysm treatment after subarachnoid hemorrhage. *World Neurosurg*. 2012; 77:311–5.
14. Phillips T, Dowling R, Yan B, Laidlaw J, Mitchell P. Does Treatment of Ruptured Intracranial Aneurysms Within 24 Hours Improve Clinical Outcome? *Stroke*. 2011; 42:1936–45.
15. Rawal S, Alcaide-Leon P, Macdonald RL, et al. Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid hemorrhage: inconsistent results of early treatment within 1 day. *J Neurol Neurosurg Psychiatry*. 2017; 88:241–8.

16. Cagnazzo F, Gambacciani C, Morganti R, Perrini P. Aneurysm rebleeding after placement of external ventricular drainage: a systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2017; 159:695–704.
17. van Lieshout JH, Pumplün I, Fischer I, et al. Volume of cerebrospinal fluid drainage as a predictor for pretreatment aneurysmal rebleeding. *J Neurosurg*. 2018; 128:1778–84.
18. Berkhemer OA, Fransen PSS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *N Engl J Med*. 2015; 372:11–20.
19. Germans MR, Hoogmoed J, van Straaten HAS, et al. Time intervals from aneurysmal subarachnoid hemorrhage to treatment and factors contributing to delay. *J Neurol* 2014; 261:473–479
20. Germans MR, Coert BA, Vandertop WP, et al. Time intervals from subarachnoid hemorrhage to rebleed. *J Neurol* 2014; 261:1425–1431
21. Linzey JR, Williamson C, Rajajee V, Sheehan K, Pandey AS, Thompson BG. Twenty-four-hour emergency intervention versus early intervention in aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2017; 122:1297–303.
22. Hillman J, Fridriksson S, Nilsson O, Yu Z, Säveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg*. 2009; 97:771–8.
23. Baharoglu M, Germans M, Rinkel G, et al. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage. *Cochrane Database Syst Rev*. 2013;30:CD001245.
24. Post R, Germans MR, Boogaarts HD, et al. Short-term tranexamic acid treatment reduces in-hospital mortality in aneurysmal sub-arachnoid hemorrhage: A multicenter comparison study. *PLoS One*. 2019; 14:e0211868.
25. Germans MR, Post R, Coert BA, et al. Ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA): study protocol for a randomized controlled trial. *Trials*. 2013; 14:143.
26. Stienen MN, Visser Meily, JM, Schweizer TA et al. Prioritization and Timing of Outcomes and Endpoints After Aneurysmal Subarachnoid Hemorrhage in Clinical Trials and Observational Studies: Proposal of a Multidisciplinary Research Group. *Neurocrit Care*. 2019; 30:S102–S113
27. Buunk AM, Groen RJM, Wijbenga RA, et al. Mental versus physical fatigue after subarachnoid hemorrhage: differential associations with outcome. *Eur J Neurol*. 2018; 25:e1313–e113.
28. Buunk AM, Spikman JM, Metzemaekers JDM, et al. Return to work after subarachnoid hemorrhage: The influence of cognitive deficits. *PLoS One*. 2019; 14:e0220972.
29. Lindgren A, Vergouwen M, Van Der Schaaf I, et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid hemorrhage. *Cochrane Database Syst Rev*. 2018; 8:CD003085.
30. Koivisto T, Vanninen R, Hurskainen H, et al. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. *Stroke*. 2000; 31:2369–77.

31. Bakker NA, van Dijk JMC, Veeger NJGM. ISAT: End of the debate on coiling versus clipping? *Lancet*. 2015; 385:2250–1.
32. Darsaut TE, Jack AS, Kerr RS, et al. International subarachnoid aneurysm trial - ISAT Part II: Study protocol for a randomized controlled trial. *Trials*. 2013; 14:1–8.
33. Darsaut TE, Roy D, Weill A. A randomized trial of endovascular versus surgical management of ruptured intracranial aneurysms: Interim results from ISAT 2. *Neurochirurgie*. 2019; 65:370–376
34. Al-Khindi T, Loch Macdonald R, Schweizer T. Cognitive and Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. *Stroke*. 2010; 41:e519–e536
35. Egeto P, Loch Macdonald R, Ornstein TJ, Schweizer TA. Neuropsychological function after endovascular and neurosurgical treatment of subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurosurg*. 2018; 128:768–776.
36. van Lieshout JH, Verbaan D, Donders R, et al. Periprocedural aneurysm rerupture in relation to timing of endovascular treatment and outcome. *J Neurol Neurosurg Psychiatry*. 2019; 90:363–5.
37. Zhao B, Rabinstein A, Murad M, Lanzino G, Panni P, Brinjikji W. Surgical and endovascular treatment of poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurosurg Sci*. 2017; 61:403–15.
38. Han Y, Ye F, Long X, et al. Ultra-Early Treatment for Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. *World Neurosurg*. 2018; 115:e160–71.
39. Philip White. Treatment of poor-grade subarachnoid hemorrhage trial 2. TOPSAT 2. <https://doi.org/10.1186/ISRCTN15960635>. June 2016. Accessed 11-11-2019

Appendices

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SUMMARY

Spontaneous subarachnoid hemorrhage (SAH) is a devastating type of stroke, with the most frequent cause being a ruptured intracranial aneurysm. Although case-fatality rates of patients with SAH has decreased over the past decades due to improvements in diagnostics and treatment, mortality and morbidity rates remain high. Aim of this thesis was to broaden knowledge about aneurysm rupture and to gain more insight in predictive factors for rebleeding and the patients' outcome after SAH.

There is an on-going search for conditions that induce SAH. A seasonal pattern of SAH is shown in a large meta-analysis of the literature, but its explanation and relationship with the weather remains undecided. In **chapter 2**, we reviewed the Groningen Subarachnoid Hemorrhage cohort on the seasonal incidence of SAH and the association between SAH and local meteorological factors. We used regional data of the Royal Netherlands Meteorological Institute and compared SAH incidences over the year. We found a significantly decreased incidence of aneurysmal SAH in July, which could not be explained by atmospheric pressure and temperature variations. Furthermore, we found that atmospheric pressure variations were significantly associated with aneurysmal SAH. In particular, the pressure change on the second and third day before the ictus was independently correlated to a higher incidence of aneurysmal SAH. These findings can be indicative to further elucidate the pathophysiology of aneurysm rupture.

A rebleeding is one of the most feared complications after an aneurysmal SAH (aSAH), with reported mortality rates up to 60%. Exact incidence rates of rebleeding are not known and there is little knowledge about risk factors for rebleeding. Therefore, in **chapter 3**, we aimed to identify rebleeding rates and risk factors for rebleeding in relation to time after ictus. 1205 patients with an aneurysmal SAH from the Groningen Subarachnoid Hemorrhage cohort were included. We found that cumulative in-hospital rebleeding rates were 5.8% $\leq$ 24 hours, and 1.2% in the time frame 24–72 hours after ictus, with a majority of the rebleedings occurring in the first 8 hours after the ictus. A mFisher score of 3–4 was the strongest independently associated risk factor for early rebleeding after SAH. Furthermore, the initiation of external cerebrospinal fluid drainage and a larger aneurysm size were also associated with a higher risk of rebleeding. Our findings suggest that in patients with a mFisher score of 3–4, aneurysm repair should be instigated as soon as possible to prevent an, often fatal, rebleeding. Furthermore, in these patients, CSF-drainage should preferably be instigated after successful aneurysm repair.

Currently, early prediction of outcome after SAH lacks accuracy despite multiple studies addressing this issue. The clinical condition of the patient on admission as assessed by

the World Federation of Neurosurgical Societies (WFNS) grading scale is currently considered the golden standard. However, timing of the clinical assessment is subject to debate, as is the contribution of additional predictors. In **chapter 4**, we investigated the optimal timing of neurological assessment for prediction of outcome after SAH, either the WFNS score assessed at admission or assessed after neurological resuscitation (rWFNS). We included all 1640 SAH patients of the Groningen Subarachnoid Hemorrhage Cohort admitted between 1998-2014, also patients with a non-aneurysmal SAH or an intracranial artery dissection. We found that the rWFNS is a better predictor for functional outcome after SAH compared to the WFNS on admission, and also the most important predictor. Furthermore, we identified four other predictors for short-term clinical outcome: higher age, larger aneurysm, higher modified Fisher grade and the presence of an intracerebral hematoma. Together, these predictors have excellent prognostic value in our cohort regarding the discrimination between poor and good outcome 2 months after SAH.

In **chapter 5**, we continued to improve prediction of outcome by development and validation of a prognostic model for early prediction of outcome after aSAH. For development of the model we used the aSAH patients of the Groningen Subarachnoid Hemorrhage cohort. For validation of the model, we used the most recent cohort of 224 aSAH patients of the Groningen Subarachnoid Hemorrhage cohort (temporal validation), and the International Subarachnoid Aneurysm Trial (ISAT) cohort of 2143 aSAH patients (external validation). Performance of the model was examined in terms of discrimination and calibration. The final model included four predictors independently associated with poor outcome after two months: age, rWFNS-grade, aneurysm size and Fisher grade. The model showed good discrimination and calibration in both the temporal as the external validation cohort. The SAFIRE-grading scale was derived from the final model: (S)ize of the aneurysm, (A)ge, (F)isher grade, WFNS after (RE)suscitation, which is an accurate, generalizable and easily applicable model for early prediction of clinical outcome after aSAH. The bedside grading scale identifies poor-grade patients better compared to the nowadays used WFNS-score, and can therefore aid decision-making regarding treatment at an early stage.

To prevent early rebleeding, treatment of the aneurysm by neurosurgical clipping or endovascular coiling should be performed. ISAT is the only large trial comparing the two treatment modalities, which showed that coiling is associated with better outcomes after 1 year. It is known that in the ISAT study population significantly more patients in the neurosurgical group died before treatment could be instigated, compared to the endovascular group. A possible explanation for this difference is the longer time between randomization and treatment in this particular group, which kept these patients longer

at risk for rebleeding. In **chapter 6**, we therefore assessed the impact of this treatment delay on the outcome of ISAT. The results show that after exclusion of pre-treatment deaths, coiling was favorable over clipping at 1-year follow-up. After 5 years however, no significant differences were observed, neither in death or dependency. Time between randomization and treatment was significantly longer in the clipping arm and more patients in this arm died as a result of rebleeding. These additional analyses show that after correction for treatment delay, coiling and clipping are comparable in long term based on the ISAT data. The high number of pre-treatment deaths in the clipping group highlights the importance of urgent aneurysm treatment to prevent early rebleeding.

All together, this shed light on the seasonal incidence of SAH and the relationship with meteorological factors. Furthermore, it aids to the prediction of rebleeding and short-term outcome after aSAH. Based on this thesis, a new treatment paradigm for the acute phase of aSAH is proposed, recommending treatment of patients at high risk for rebleeding on an emergency base. Furthermore, this thesis highlights the importance of accurate identification of patients in a poor clinical condition for decisions regarding (timing of) treatment. The SAFIRE grading scale is proposed as a new tool to assess the patients' outcome soon after the ictus. Last, it revealed the impact of treatment delay and rebleeding on the outcomes of ISAT, and found that after correcting for this, coiling and clipping could be considered comparable in long term based on ISAT data. All together, these new insights can lead to improved treatment of patients with aSAH and a further decline in mortality and morbidity rates.

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Een spontane subarachnoidale bloeding (SAB) is een verwoestende vorm van beroerte, meestal veroorzaakt door een gebarsten intracerebraal aneurysma. Ondanks dat er de laatste decennia een daling van de sterfte ten gevolge van een SAB wordt gezien, blijft deze ziekte geassocieerd met hoge morbiditeit en mortaliteit. Doel van dit proefschrift was om de kennis rondom het optreden van een SAB te verbreden, meer inzicht te krijgen in risicofactoren voor het optreden van een recidief bloeding en om de uitkomst van de patiënt na een SAB beter te kunnen voorspellen.

Er is nog veel onduidelijk over het luxerende moment van een SAB. Al langer werd een seizoensgebonden patroon in SAB-incidentie gezien en dit is recent bevestigd in een grote meta-analyse. Er is echter weinig bekend over de achterliggende oorzaak hiervan en een mogelijke relatie met het weer. In **hoofdstuk 2** is er binnen het Groningse SAB-cohort gekeken naar de verschillen in incidentie van SAB door het jaar heen en de associatie met meteorologische factoren. We hebben gebruik gemaakt van regionale data van het Koninklijk Nederlands Meteorologisch Instituut en de SAB-incidentie over het jaar berekend. De resultaten laten een lagere incidentie van aneurysmale SAB's (aSAB) zien in juli, dit patroon werd niet verklaard door atmosferische druk- en/of temperatuurverschillen. Wel werd er een associatie gezien tussen dagelijkse atmosferische drukverschillen en het optreden van een aSAB, met name twee tot drie dagen na grote dagelijkse drukverschillen trad er vaker een SAB op. Deze bevindingen kunnen een aanknopingspunt zijn voor verder onderzoek naar de pathofysiologie van een aneurysma ruptuur.

Een recidief bloeding is een van de meest gevreesde complicaties na een SAB, met daarbij een sterfte oplopend tot 60%. Incidentie cijfers van een recidief bloeding wisselen sterk in de literatuur en daarnaast is er weinig bekend over risicofactoren voor een recidief bloeding. Daarom wordt in **hoofdstuk 3** binnen het Groningse SAB-cohort de incidentie van recidief bloedingen in relatie tot tijd na de initiële aSAB en risicofactoren voor het optreden hiervan onderzocht. In deze studie werden 1205 patiënten met een aSAB geïnccludeerd. Uit de resultaten blijkt dat het aantal recidief bloedingen in het ziekenhuis gedurende de eerste 24 uur 5.8% bedraagt, in de periode 24-72 uur na initiële SAB is dit 1.2%. De sterkste onafhankelijke voorspeller voor een vroege recidief bloeding was een mFisher score van 3-4. Daarnaast was ook het plaatsen van een externe cerebrospinale vloeistofdrain en een groter aneurysma geassocieerd met een vroege recidief bloeding. Onze resultaten suggereren dat in patiënten met een hoge mFisher score (3-4), behandeling van het aneurysma zo snel mogelijk dient plaats te vinden om een vaak fatale recidief bloeding te voorkomen.

In de praktijk blijft het lastig om een goede voorspelling te doen omtrent de klinische uitkomst na een SAB. Momenteel is de klinische conditie van de patiënt (WFNS-score) ten tijde van aankomst in het ziekenhuis de meest gebruikte maat hiervoor, echter we weten dat dit niet volledig accuraat is. Met name het moment waarop de WFNS-score bepaald dient te worden voor een goede inschatting van de uitkomst, is een onderwerp van discussie. In **hoofdstuk 4** hebben we gekeken of de WFNS-score bij binnenkomst of de WFNS na neurologische resuscitatie (rWFNS) een betere voorspeller is voor uitkomst van deze patiënten. Voor deze studie includeerden we alle 1640 SAB-patiënten van het Groninger SAB-cohort, ook de patiënten met een non-aneurysmale SAB of een SAB op basis van een dissectie aneurysma. Het bleek dat de rWFNS een betere voorspeller is voor klinische uitkomst na SAB in vergelijking met de conventionele WFNS bij aankomst. De rWFNS was tevens de sterkste voorspeller voor uitkomst na SAB. Daarnaast was ook hogere leeftijd, een groter aneurysma, een hogere mFisher score en de aanwezigheid van een intracerebraal hematoom geassocieerd met een slechtere uitkomst na 2 maanden. Samen hebben deze 5 voorspellers een goede prognostische waarde in ons cohort om de patiënten met een goede en slechte uitkomst van elkaar te onderscheiden.

In **hoofdstuk 5** borduren we voort op de resultaten van hoofdstuk 4, waarbij wij een predictiemodel hebben ontwikkeld en gevalideerd om vroeg in het behandeltraject de klinische uitkomst te kunnen voorspellen. Voor de ontwikkeling van het model werd het Groninger SAB-cohort tot 2014 gebruikt. Voor validatie van het model werd gebruikt gemaakt van het meest recente Groninger SAB-cohort (jaren 2014-2017) en het ISAT-cohort (International Subarachnoid Aneurysm Trial) voor externe validatie. Het uiteindelijk model bestond uit vier onafhankelijke voorspellers voor slechte uitkomst na een aSAB: leeftijd, de rWFNS-graad, aneurysma grootte en de Fisher graad. Het model laat een goede discriminatie en kalibratie zien, in zowel ons eigen cohort als het ISAT-cohort. De SAFIRE schaal ((S)ize of the aneurysm, (A)ge, (F)isher grade, WFNS after (RE)suscitation) werd verkregen uit het predictie model. Dit is een makkelijke en accurate schaal om uitkomst na een aSAB te voorspellen, het voorspelt beter dan de huidige WFNS-graad alleen. De SAFIRE-schaal kan in de klinische praktijk gebruikt worden om patiënten te onderscheiden, behandeling te individualiseren en om patiënt en familie beter te kunnen informeren omtrent de korte termijn prognose na het doormaken van een SAB.

Om te voorkomen dat er een recidief bloeding optreedt na een initiële aSAB, moet het aneurysma behandeld worden door middel van het neurochirurgisch 'clippen' of het endovasculair 'coilen'. De enige grote trial die het effect van beide behandelingen heeft vergeleken is ISAT, waaruit bleek dat coilen een betere klinische uitkomst geeft na 1 jaar follow-up. Het is bekend dat in ISAT significant meer patiënten uit de neurochirurgische

groep waren overleden voordat de geplande behandeling daadwerkelijk kon worden uitgevoerd, in vergelijking tot de endovasculaire groep. Een mogelijke verklaring hiervoor is de langere tijd tussen de toewijzing van behandeling (via randomisatie) en de daadwerkelijke uitvoer van de behandeling in de neurochirurgische groep, waardoor deze patiënten langer aan het risico op een recidief bloeding werden blootgesteld. In **hoofdstuk 6** hebben we daarom gekeken naar de vertraging in behandeling en het effect hiervan op de resultaten van ISAT. De resultaten lieten zien dat na exclusie van de overledenen vóór de behandeling, coilen een betere klinische uitkomst na 1 jaar geeft. Echter, na 5 jaar is er geen significant verschil meer te zien tussen coilen en clippen. Tijd tussen randomisatie en behandeling was significant langer in de clipping groep, met ook een significant hogere sterfte als gevolg van een recidief bloeding. Uit deze aanvullende analyses blijkt dat wanneer er gecorrigeerd wordt voor vertraging in behandeling, de lange termijn uitkomsten van coilen en clippen op basis van de ISAT-resultaten vergelijkbaar zijn. Het hoge percentage overledenen voor de behandeling in de clipping groep benadrukt het belang van snel behandelen om een vroege recidief bloeding te voorkomen.

Al met al dragen de resultaten van dit proefschrift bij aan de kennis over de seizoensgebonden incidentie van een SAB en de relatie met meteorologische factoren. Daarnaast geeft het inzicht in de voorspelling van vroege recidief bloedingen en de uitkomst na een SAB. Gebaseerd op de resultaten in dit proefschrift wordt er een nieuwe aanpak in de acute fase behandeling van aSAB voorgesteld, waarin wordt aanbevolen patiënten met een verhoogd risico op recidief bloeding te behandelen op spoed basis. Daarnaast wordt het belang van een goede voorspelling van uitkomst na aSAB benadrukt om juiste beslissingen te nemen met betrekking tot (tijdstip van) behandeling. De 'SAFIRE schaal' wordt als nieuw instrument geïntroduceerd voor de vroege voorspelling van uitkomst na aSAB. Tenslotte laat dit proefschrift de impact van vertraagde behandeling en recidief bloedingen op de resultaten van ISAT zien, waarbij er werd gevonden dat na correctie hiervan, coilen en clippen op lange termijn, op basis van de ISAT-data, vergelijkbaar zijn. Tezamen kunnen deze nieuwe inzichten leiden tot een verbetering van de behandeling van SAB-patiënten en een verdere daling van mortaliteit en morbiditeit.

LIST OF ABBREVIATIONS

aHR	adjusted hazard ratio
aSAH	aneurysmal subarachnoid hemorrhage
AUC	area under the curve
CSF	cerebrospinal fluid
CI	confidence interval
CT	computerized tomography
CTA	computerized tomographic angiography
DCI	delayed cerebral ischemia
DSA	digital subtraction angiography
EVT	endovascular treatment
GCS	Glasgow Coma Scale
HR	hazard ratio's
ICU	intensive care unit
IQR	interquartile range
IRR	incidence rate ratio
ISAT	International Subarachnoid Aneurysm Trial
ITT	intention to treat
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NNT	number needed to treat
NST	neurosurgical treatment
OR	odds ratio
ROC	receiver operating chart
RR	relative risk
SAH	subarachnoid hemorrhage
WFNS	World Federation of Neurosurgical Societies

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maar bovenal over het kritisch zijn en blijven. Het kan altijd beter! Zonder jouw enorme drive en onuitputtelijke enthousiasme, had dit proefschrift hier niet gelegen. Heel veel dank daarvoor.

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ABOUT THE AUTHOR

Carlina Elizabeth van Donkelaar (Karlijn) was born on January 6th 1994 in Gorinchem, the Netherlands. She lived in Werkendam the first 14 years of her life. After three years of secondary school at the Gymnasium Camphusianum, she moved with her parents and sister to Koekange, a little village in the province of Drenthe. In 2011 she graduated at the Gymnasium in Meppel after which she started Medical school at the University of Groningen. During her bachelor's degree, she became interested in research and started with a pilot project at the department of Intensive Care Medicine, followed by a project at the department of Neurosurgery. At the latter, she performed her scientific master thesis named 'predictive factors of rebleeding after aneurysmal subarachnoid hemorrhage' under supervision of prof. dr. Marc van Dijk and dr. Bakker, which eventually resulted in a PhD-trajectory. Karlijn combined her research with clinical internships at the University Medical Center Groningen and 'Ziekenhuis Groep Twente' in Almelo. The last part of her PhD took place in Oxford, United Kingdom, where she worked at the Centre for Statistics in Medicine under supervision of miss Jacqueline Birks and prof. dr. Andrew Molyneux. In January 2019, she obtained her MD degree and started working as a resident at the department of Obstetrics and Gynecology at the Medical Center Leeuwarden. Her PhD trajectory resulted in this thesis, which she will defend on the 6th of July 2020.

LIST OF PUBLICATIONS

van Donkelaar CE, de Haan JMH, Lange JFM, de Vries M, Horváth B. Pseudo-wound infection after a caesarean section: Case report of unrecognized Pyoderma Gangrenosum. *Int J Surg Case Rep.* 2020; 69:79-82.

van Donkelaar CE, Bakker NA, Birks J, Clarke A, Sneade M, Kerr RSC, Veeger NJGM, van Dijk JMC, Molyneux AJ. Impact of Treatment Delay on Outcome in the International Subarachnoid Aneurysm Trial. *Stroke.* 2020; 51:1600-1603.

van Donkelaar CE, Bakker NA, Birks J, Veeger NJGM, Metzemaekers JDM, Molyneux AJ, Groen RJM, van Dijk JMC. Prediction of Outcome After Aneurysmal Subarachnoid Hemorrhage. *Stroke.* 2019; 50:837-844

van Donkelaar CE, Potgieser ARE, Groen H, Foumani M, Abdulrahman H, Sluijter R, van Dijk JMC, Groen RJM. Atmospheric Pressure Variation is a Delayed Trigger for Aneurysmal Subarachnoid Hemorrhage. *World Neurosurg.* 2018; 112:e783-e790.

van Donkelaar CE, Bakker NA, Veeger NJ, Uyttenboogaart M, Metzemaekers JD, Eshghi O, Mazuri A, Foumani M, Luijckx GJ, Groen RJ, van Dijk JM. Prediction of outcome after subarachnoid hemorrhage: timing of clinical assessment. *J Neurosurg.* 2017; 126:52-59.

van Donkelaar CE, Dijkland SA, van den Bergh WM, Bakker J, Dippel DW, Nijsten MW, van der Jagt M. Early Circulating Lactate and Glucose Levels After Aneurysmal Subarachnoid Hemorrhage Correlate With Poor Outcome and Delayed Cerebral Ischemia: A Two-Center Cohort Study. *Crit Care Med.* 2016; 44:966-72.

van Donkelaar CE, Bakker NA, Veeger NJ, Uyttenboogaart M, Metzemaekers JD, Luijckx GJ, Groen RJ, van Dijk JMC. Predictive Factors for Rebleeding After Aneurysmal Subarachnoid Hemorrhage: Rebleeding Aneurysmal Subarachnoid Hemorrhage Study. *Stroke.* 2015; 46:2100-6.